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Parathyroid tumors and related disorders

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Primary hyperparathyroidism (P-HPT) is a common endocrine disorder that occurs as a result of adenomas (80–85%), hyperplasias (10–15%) or carcinomas (<1%) of the parathyroid glands. Molecular genetic analyses of heritable P-HPT syndromes have provided considerable insight into the understanding of sporadic parathyroid tumors and hyperplasias. This review will focus on the criteria for classification of parathyroid proliferative disorders and will highlight our understanding of these lesions at the molecular level. Advances in radiological imaging techniques together with the rapid intraoperative parathyroid hormone assay will be reviewed with respect to current treatment approaches for P-HPT.
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Primary hyperparathyroidism (P-HPT) is an ancient disease with one of the earliest documented cases described in a 25- to 35-year-old woman discovered in an early Neolithic cemetery.[1] Plain films and CT scans showed changes consistent with HPT, including significant demineralization of the skeleton with a 'salt and pepper' appearance of the skull. Histological examination revealed significant enlargement of the Haversian canals in compact bone, broad based endosteal resorption zones and 'cookie bite' defects of the trabecular surface of cancellous bone.

In the first quarter of the 20th century, reports of two patients (Albert G (Vienna) and Captain Charles Martell (Boston)) identified tumors of the parathyroid glands as being responsible for widespread demineralization of the skeleton, cystic disease of bone and recurrent renal stones.[2,3] The case of Captain Charles Martell is particularly well known. This patient was subjected to multiple cervical explorations in attempts to find a parathyroid tumor that was ultimately located within the mediastinum. Amazingly, Captain Martell lost 7 inches in height as a result of severe bone disease during the 13-year course of his illness.

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Epidemiology and clinical aspects

Primary hyperparathyroidism emerged from relative obscurity before the 1970s to become the third most common endocrine disorder in more recent times.[4,5] This dramatic change was brought about by the introduction of automated serum calcium measurements in mid-1974. As a result of this type of screening, the age-adjusted incidence rates of P-HPT increased from 15.8 (1970–74) to 82.5 cases (1974–82) per 100 000 person years for males and females.[6] Since that time, the incidence rates have decreased. Numerous hypotheses have been advanced to explain the progressive decline, including the 'sweeping' effects of screening, the use of estrogen replacement in postmenopausal women, calcium and vitamin D dietary supplementation and the use of therapeutic head and neck irradiation in the 1930s and 1940s, which could have accounted for the 'epidemic' of hyperparathyroidism observed in the late 1970s and 1980s.

Primary hyperparathyroidism predominates in women with a female to male ratio of 3–4:1 and an average age at diagnosis of 55 years. The clinical presentations in recent series have changed from those dominated by severe bone and kidney disease to those characterized by lack of symptoms or by fatigue, weakness, depression and gastrointestinal symptoms, including constipation, nausea and dyspepsia.[5]

The term P-HPT refers to the inappropriate overproduction of parathyroid hormone (PTH), resulting in abnormal calcium homeostasis. High levels of

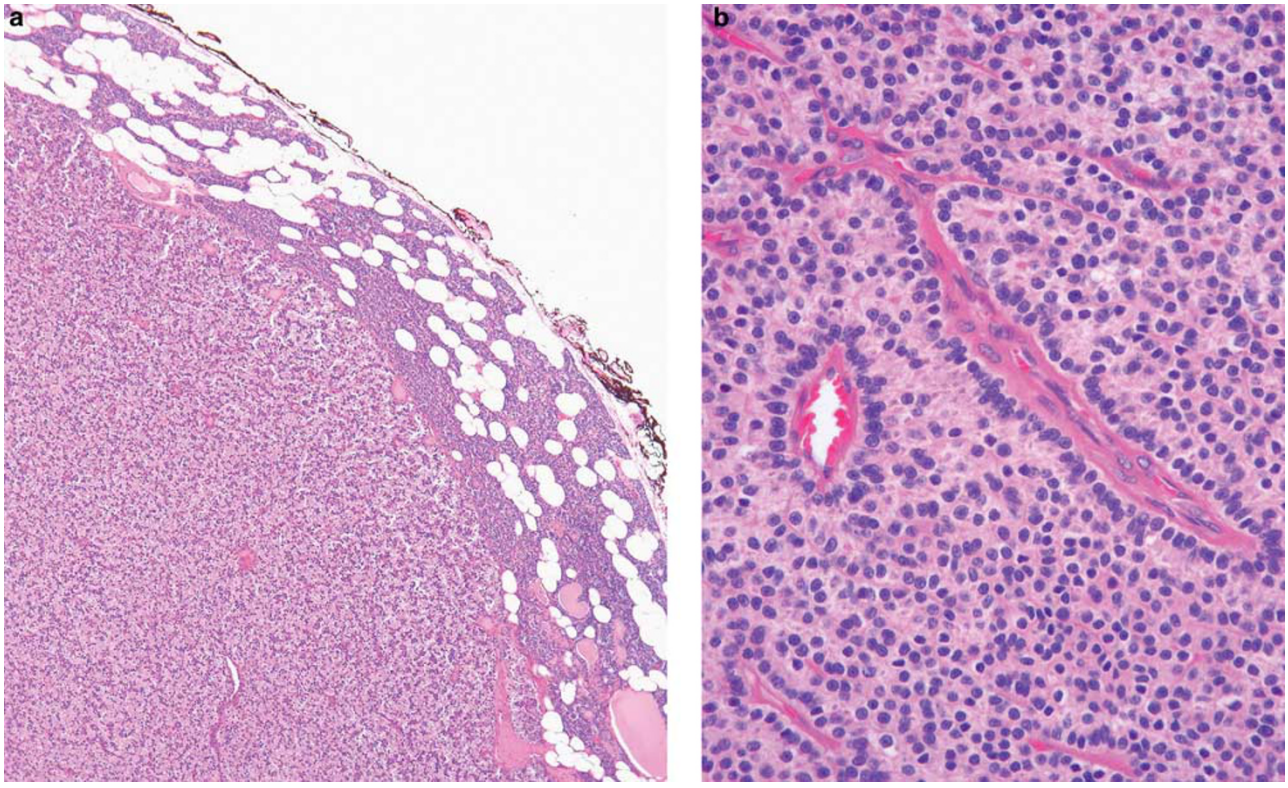

Figure 1 (**a**) Parathyroid adenoma, chief cell type. The tumor (left) is surrounded by a rim of normocellular parathyroid gland. (**b**) Parathyroid adenoma, chief cell type. The tumor cells have round to ovoid nuclei with densely stained chromatin and a palisaded arrangement around blood vessels.

PTH lead to increased renal resorption of calcium, phosphaturia, increased synthesis of 1,24 $(OH)_2D_3$ and increased bone resorption.[5] Typically, patients have evidence of hypercalcemia, hypophosphatemia, hypercalciuria, increased levels of PTH and normal levels of PTH-related protein. Occasional patients with normocalcemic hyperparathyroidism have also been described.[7] P-HPT may result from adenoma/single-gland disease (80–85%), hyperplasia/multi-gland disease (10–15%) or carcinoma (<1%).[8] If the frequencies of these disorders are determined by intraoperative PTH (IOPTH) assays with postoperative restoration of eucalcemia, hyperplasia becomes considerably less common.[9] Rare cases of apparent P-HPT may result from the paraneoplastic production of PTH by nonparathyroid tumors,[10] whereas most cases of malignancy-associated hypercalcemia result from the paraneoplastic production of PTH-related protein.[11]

Parathyroid adenoma

Parathyroid adenomas are benign neoplasms composed of chief cells, oncocytes or transitional oncocytes with frequent admixtures of these cell types.[12,13] Although most adenomas involve a single gland, occasional cases of double adenomas have been reported.[14] Double adenomas appear to have a nonuniform anatomic distribution with a predilection for the superior parathyroid glands, which are remnants of the fourth branchial pouch.[15] The average weight of adenomas in patients without significant bone disease is ~1 g with many <0.5 g, whereas tumors in patients with significant bone disease tend to be larger. The term 'microadenoma' refers to tumors weighing <0.1 g. Foci of cystic change tend to occur in large adenomas and are relatively common in the tumors associated with the hyperparathyroidism-jaw tumor (HPT-JT) syndrome, as discussed in a subsequent section.

Microscopically, most adenomas are composed of chief cells. Although microadenomas are nonencapsulated, larger tumors are usually surrounded by a fibrous capsule. A rim of normocellular parathyroid tissue is often present at the periphery of adenomas, although this feature may not be apparent in large tumors (Figure 1a). The component cells may be arranged in cords, nests, sheets and follicles and frequently have a palisaded arrangement around blood vessels (Figure 1b). The nuclei are round and densely stained and are typically larger than those present in the adjacent non-neoplastic parathyroid tissue. Scattered hyperchromatic and pleomorphic nuclei exhibiting so-called 'endocrine atypia' are relatively common, as are multinucleated tumor cells[13] (Figure 2). Mitotic activity may be present in up to 70% of adenomas[16] and the proliferative fraction, as

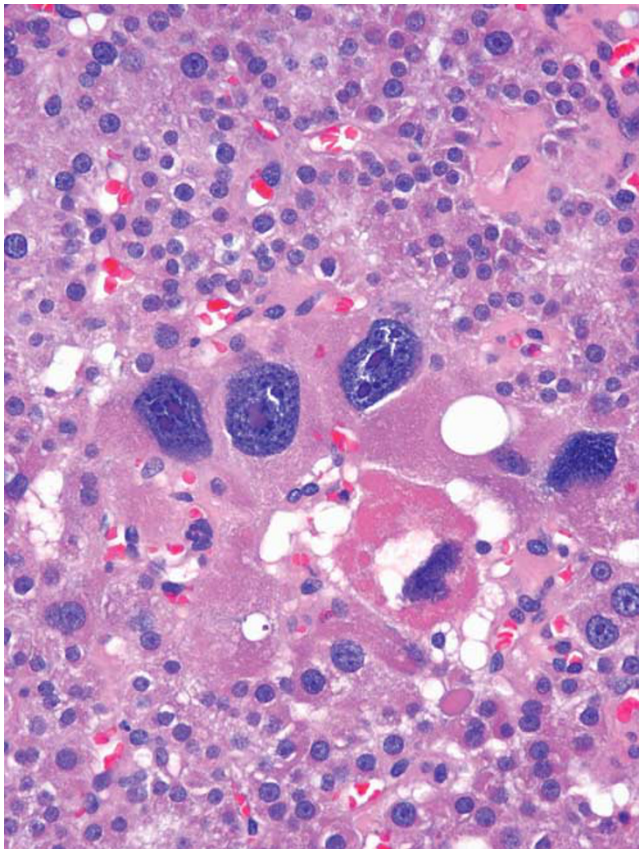

Figure 2 Parathyroid adenoma. Scattered groups of tumor cells have markedly enlarged hyperchromatic nuclei with large nucleoli (endocrine atypia) and abundant eosinophilic cytoplasm.

assessed with Ki-67, is generally $<4\%$.[17–19] The tumor cells are positive for cytokeratins, PTH and chromogranin A, whereas stains for thyroglobulin and thyroid transcription factor-1 are negative.

Some parathyroid adenomas may have a prominent follicular architecture (Figure 3a). The follicles contain a colloid-like material and may be distinguished from normal and neoplastic thyroid tissue by the presence of birefringent calcium oxalate crystals that may be present in the latter.[20] This approach is particularly useful during frozen examination. Adenoma variants include oncocytic adenomas, (Figure 3b) lipoadenomas (hamartomas) (Figure 3c) and clear cell adenomas (Figure 3d).[12,13] Lipoadenomas are characterized by the presence of abundant stromal elements including mature fat cells with myxoid change and areas of fibrosis and lymphocytic infiltration. Very rare adenomas may assume spindle cell features or may have a papillary architecture.

Adenomas represent clonal proliferations and are similar in this regard to a significant proportion of primary and secondary parathyroid hyperplasias.[21,22] One of the molecular abnormalities described in these tumors involves the cyclin D1 (*CCND1*/*PRAD1*) oncogene on 11q13. Overexpression of this oncogene results from pericentric inversion of chromosome 11p, with placement of the *CCND1* gene under the control of tissue-specific enhancer elements of the PTH gene promoter sequences. Translocations of this type were initially reported in 5% of adenomas. FISH analyses have reported translocations in up to 8% of cases.[21] However, overexpression of cyclin D1 occurs in up to 40% of adenomas, suggesting mechanisms other than translocations for overexpression. Such mechanisms could include amplification, rearrangements with other enhancers or promoters or transcriptional activation.

The *MEN1* gene on 11q13 is a tumor suppressor that encodes menin. Mutations of this gene are responsible for the development of the type1 multiple endocrine neoplasia (MEN1) syndrome.[23,24] Loss of one *MEN1* allele has been observed in up to 40% of sporadic parathyroid adenomas, with an inactivating mutation of the second allele occurring in 50% of these tumors.[21,25] Abnormalities of the *MEN1* gene have also been observed in small adenomas, suggesting that alterations of this gene represent an early event in parathyroid tumorigenesis.

Other genes including *RET*, the vitamin D receptor and the calcium-sensing receptor (*CaSR*) have also been studied for pathogeneic mutations in adenomas, but none has been found to date.[22] Comparative genomic hybridization studies have shown loss of 11q as the most frequent alteration in adenomas. In addition, losses of 1p, 6q, 9p, 11p, 13q and 15q and gains in 7, 16p and 19p occur commonly.[26]

Preoperative localization and surgical treatment

Parathyroid surgery has evolved from conventional open parathyroidectomy, with exploration of all four parathyroid glands, to minimal access open or endoscopic parathyroidectomy.[27] This evolution was made possible by the development of high-resolution radiological techniques and the development of the rapid IOPTH assay. Sonography and technetium-99m-sestamibi (^{99m}Tc-sestamibi) scintigraphy are the most commonly used imaging techniques for the demonstration of parathyroid lesions. Comparative studies have revealed similar sensitivities and specificities for the detection of adenomas with these approaches. Adenomas are almost always hypoechoic to the overlying thyroid gland on grayscale imaging.[28] Color and power Doppler imaging frequently show a characteristic extrathyroidal feeding vessel that enters the gland at one of the poles and frequently branches around the tumor producing a rim-like effect. The sensitivity of sonography for the detection of single adenomas ranges from 72 to 89%, whereas sensitivities for multiglandular disease are considerably lower.

^{99m}Tc-sestamibi is the most commonly used radiotracer for imaging of the parathyroid gland.[29] The

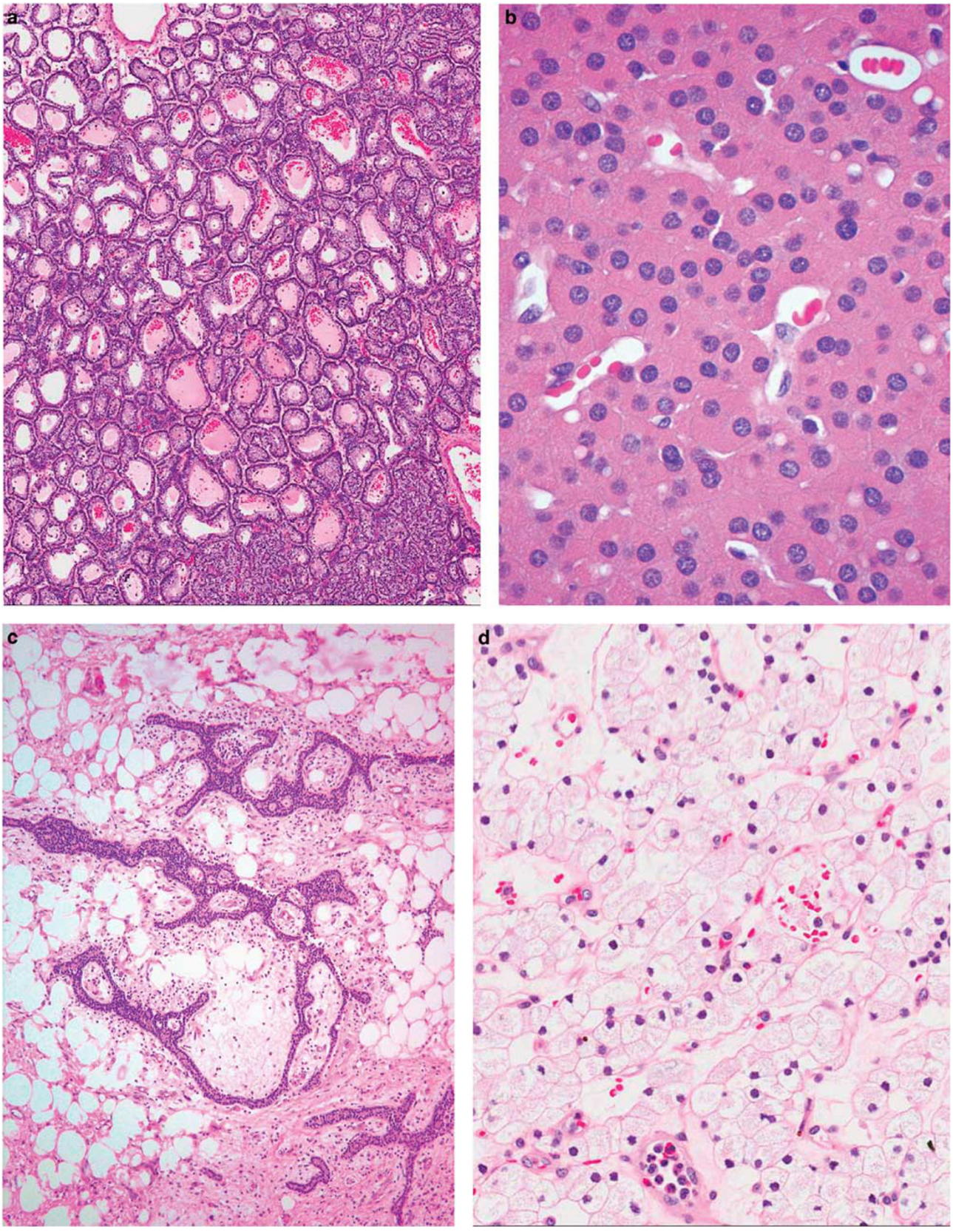

Figure 3 (**a**) Parathyroid adenoma, chief cell type. This tumor has a predominant follicular architecture with colloid-like material in many of the follicles. (**b**) Parathyroid adenoma, oncocytic type. The tumor cells have abundant granular eosinophilic cytoplasm. (**c**) Parathyroid lipoadenoma (hamartoma). The tumor cells form branching cord that are surrounded by fat cells with areas of fibrosis and chronic inflammatory cells. (**d**) Parathyroid adenoma, water-clear cell type. The tumor cells have small nuclei with dense chromatin and abundant vacuolated cytoplasm.

tracer is concentrated both by the thyroid and parathyroid glands, but hyperactive parathyroid glands typically have more avid uptake of the tracer and retain it longer than the adjacent thyroid tissue. On delayed imaging at 2 hours, the tracer is retained by abnormal parathyroid tissue but washes out of the thyroid (Figure 4). Single photon emission tomography (SPECT) with a pinhole collimator can further help to discriminate parathyroid and thyroid tissue. The sensitivity of ^{99m}Tc-sestamibi using SPECT ranges from 68 to 95% for the detection of single-gland disease, but this approach is considerably less sensitive for the identification of multiglandular disease. Modifications of the original sestamibi scan protocols include the use of radioactive iodine to subtract the thyroid image.

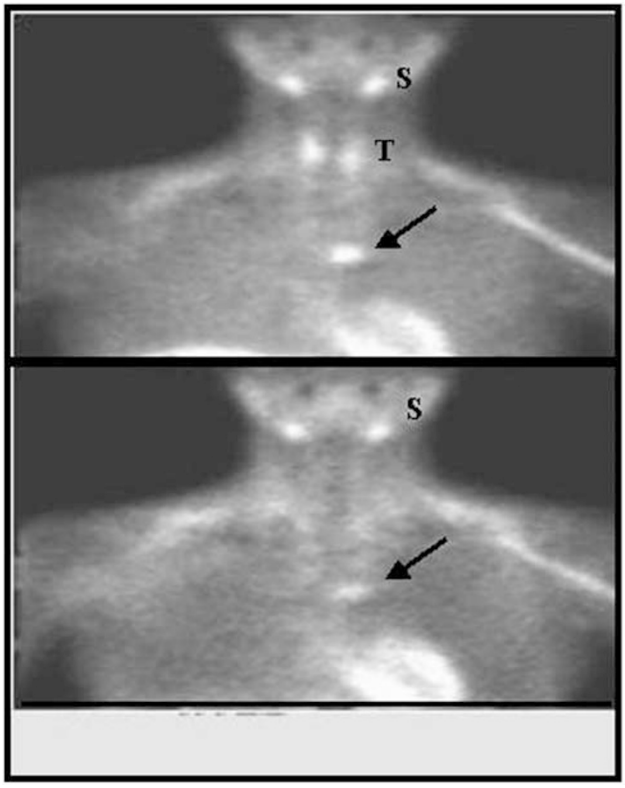

Figure 4 Delayed imaging ^{99m}Tc-Sestamibi scan (grayscale image). Top panel, initial image. Bottom panel, delayed image taken after 2 hours. Arrow indicates parathyroid adenoma. S, salivary gland, T, thyroid gland.

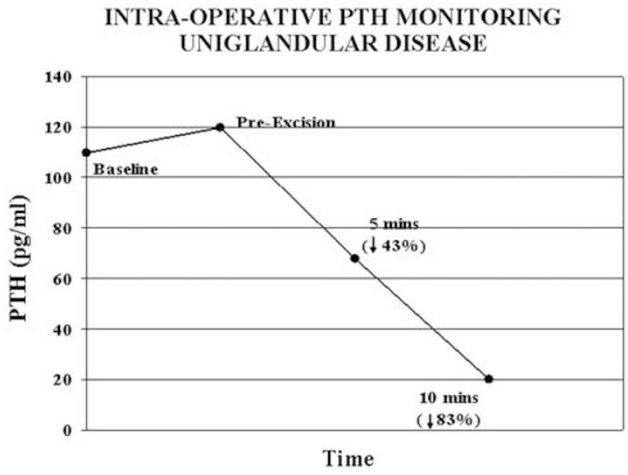

Figure 5 Intraoperative parathyroid hormone monitoring in a patient with uniglandular disease (parathyroid adenoma). There is a >50% reduction in parathyroid hormone levels 10 min after excision of the abnormal gland.

Table 1 Heritable hyperparathyroidism syndromes

Syndrome	*Gene (locus)*	*Parathyroid pathology**	*Other features*
Multiple endocrine neoplasia 1 (MEN) 1	*MEN1* (11q13)	Hyperplasia (90%)	Pituitary adenomas, pancreatic endocrine tumors, carcinoid tumors, adrenocortical tumors, facial angiofibromas, collagenomas, lipomas
Multiple endocrine neoplasia 2a (MEN 2a)	*RET* (10q11.2)	Hyperplasia (30%)	Medullary thyroid carcinoma, pheochromocytoma
Familial hypocalciuric hypercalcemia (FHH)	*CaSR*/heterozygous (3q13.3q21)	Mild hyperplasia	
Neonatal severe primary hyperparathyroidism	*CaSR*/homozygous (3q 13.3q21)	Hyperplasia	
Hyperparathyroidism-jaw tumor (HPT-JT) syndrome	*HRPT2* (1q25-q32)	Cystic adenomas, carcinoma (15%)	Ossifying jaw fibromas; renal cysts, carcinomas; Wilms' tumor
Familial isolated hyperparathyroidism	*MEN1* (11q13); *CaSR* (3q13.3-q21); *HRPT2* (1q25-q32)	Hyperplasia, carcinoma	
Familial hypercalcemic hypercalcuria (autosomal dominant mild HPT)	*CaSR*	Hyperplasia, adenoma	

*Although the term ''hyperplasia'' has been used to describe the parathyroid lesions in these syndromes, they are more closely related to adenomas since they represent clonal proliferations. For this reason, it may be preferable to refer to these cases as ''multiglandular parathyroid disease'' rather than ''hyperplasia''.

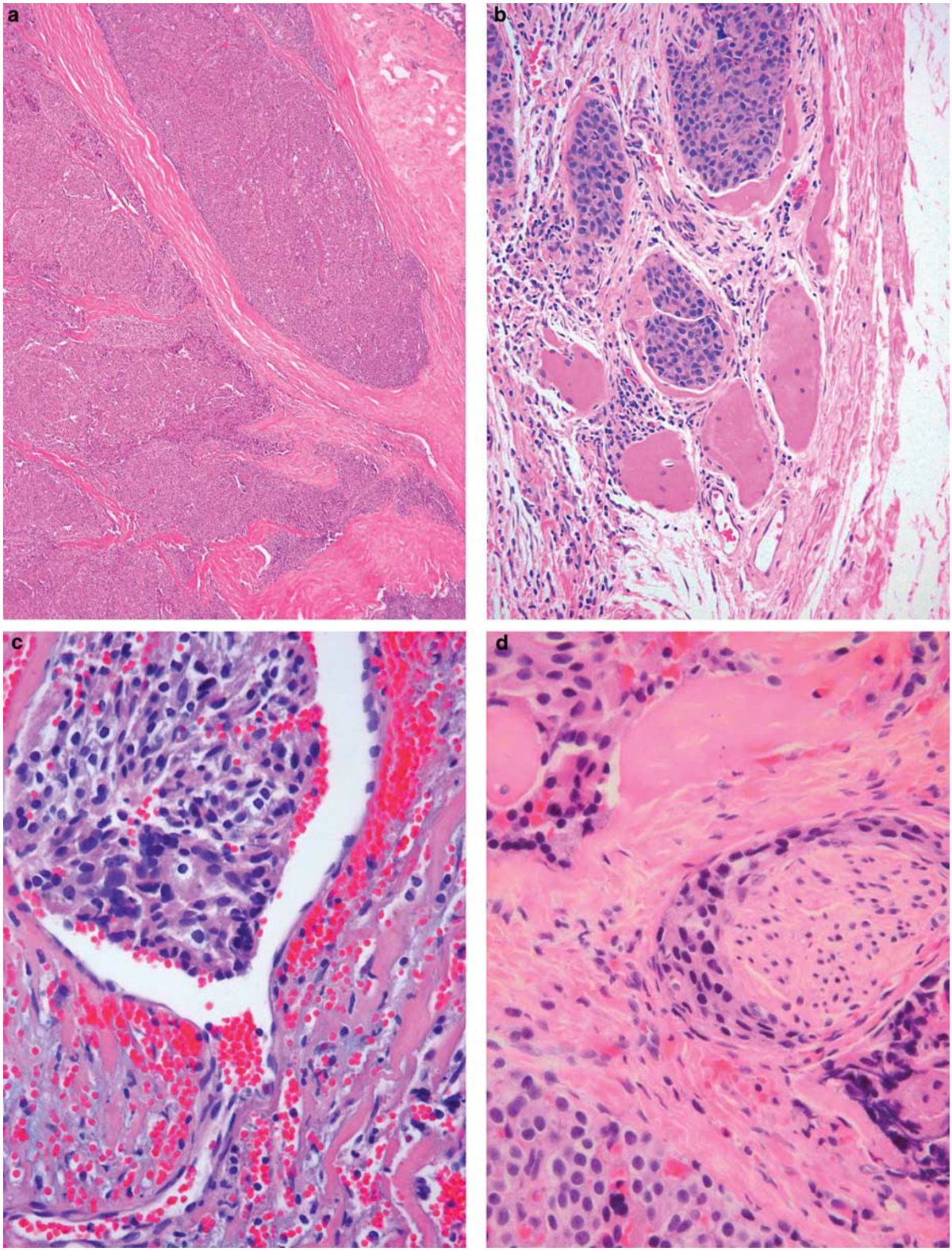

Figure 6 (**a**) Parathyroid carcinoma. The tumor is divided into cellular nodules by dense bands of fibrous connective tissue. (**b**) Parathyroid carcinoma. The tumor has invaded the adjacent skeletal muscle. (**c**) Parathyroid carcinoma. The tumor has invaded a vascular channel. (**d**) Parathyroid carcinoma. The tumor has invaded the perineural space.

The development of the rapid IOPTH assay was a major advance, as this approach could accurately confirm or refute the preoperative localization studies.[30] Overall, in-lab turnaround time for this assay averages 13–15 min. Multiple studies have confirmed the ability of IOPTH to guide

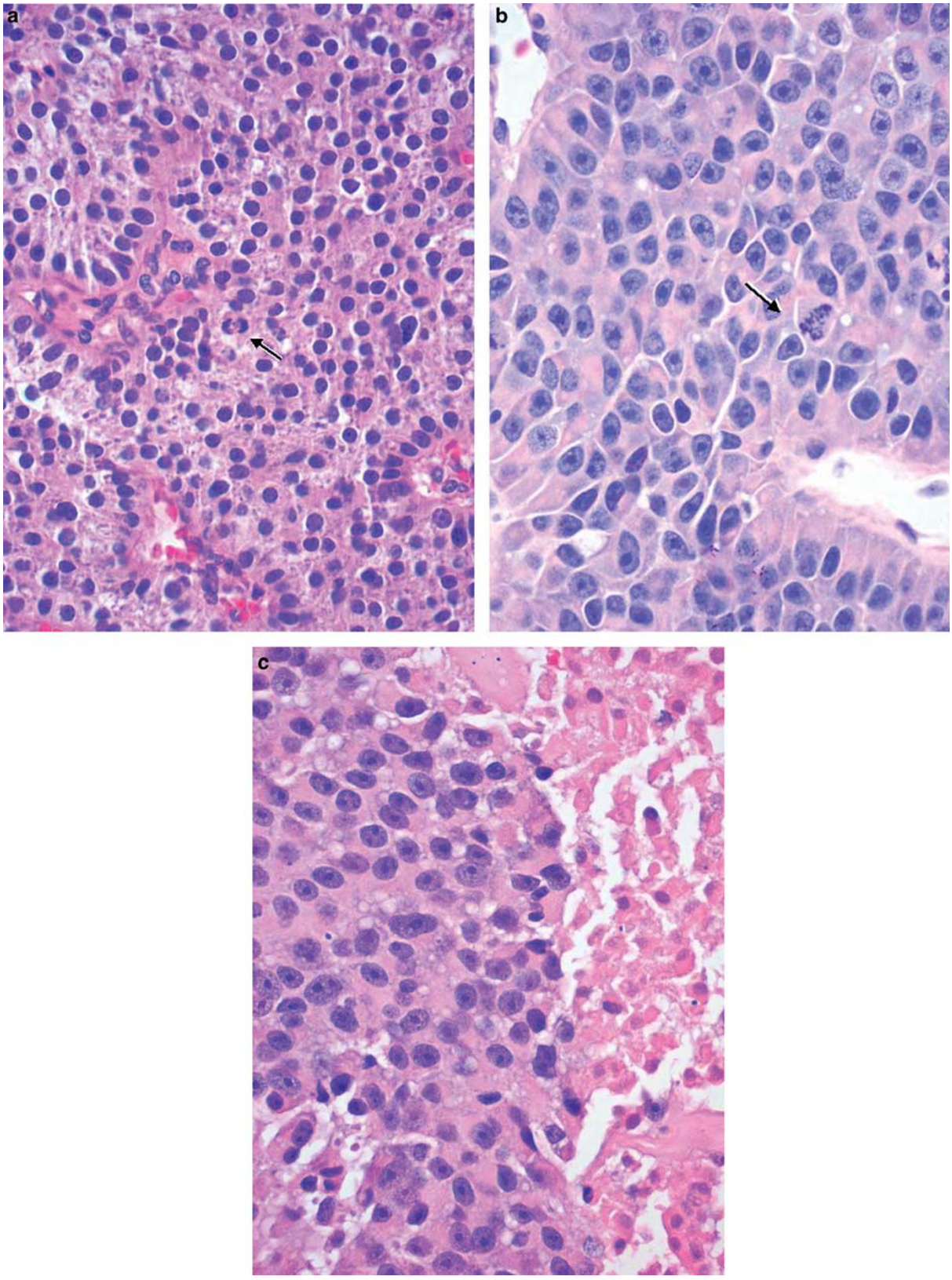

Figure 7 (**a**) Parathyroid carcinoma. This tumor is composed of mildly pleomorphic cells. A single mitotic cell (arrow) is present. Overall mitotic rate was less than 1 per 50 high-power fields. (**b**) Parathyroid carcinoma. The tumor cells have macronucleoli with an atypical mitotic figure (arrow) present in this field. (**c**) Parathyroid carcinoma. This tumor has multifocal areas of necrosis (right).

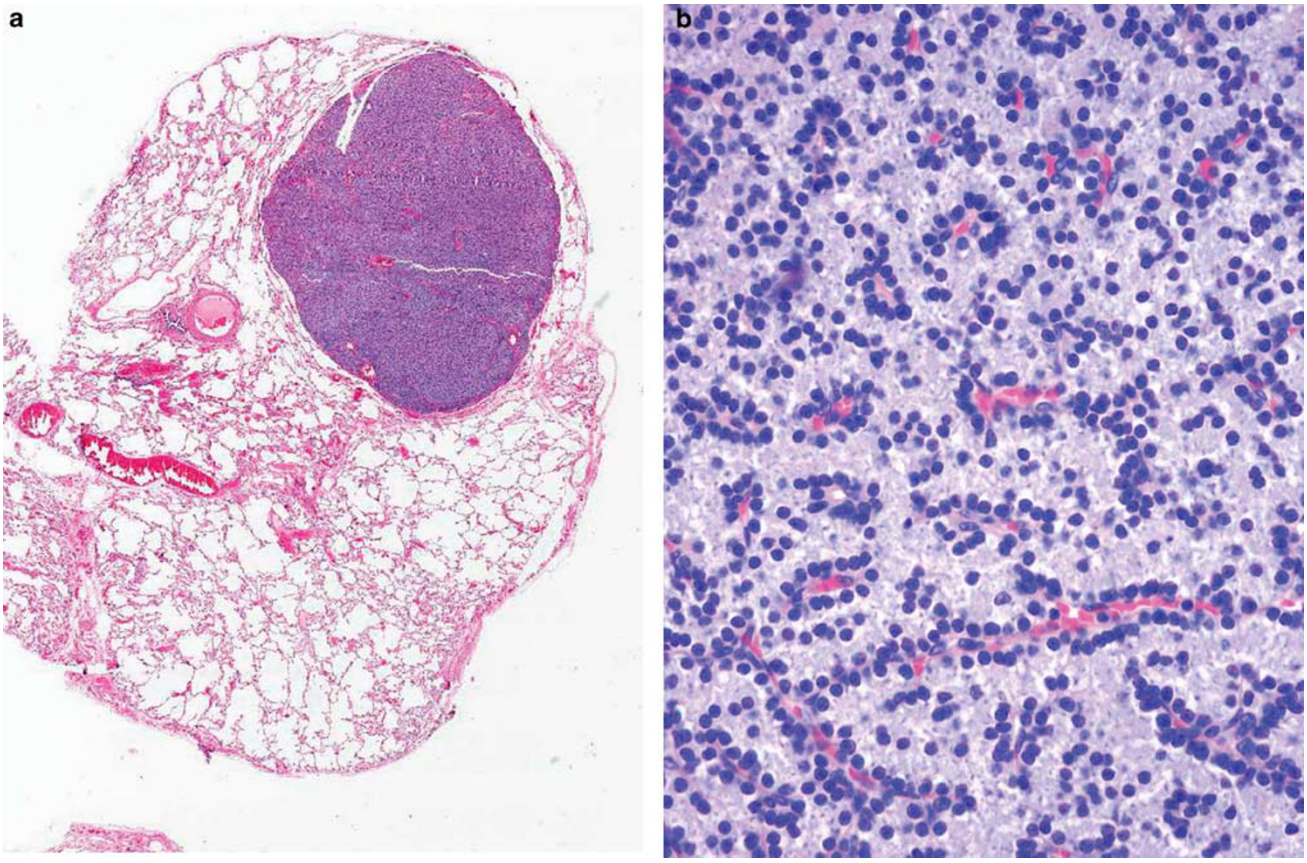

Figure 8 (**a**) Metastatic parathyroid carcinoma in lung. The metastatic tumor formed multiple circumscribed nodules. (**b**) Metastatic parathyroid carcinoma (same case as panel a). This tumor is indistinguishable from a parathyroid adenoma.

the surgeon's intraoperative decision making by accurately predicting whether or not additional hypersecreting glands remain in the neck after removal of the gland(s) identified by preoperative localization. The success of this approach is based on the fact that PTH has a half-life of <5 min. A drop in IOPTH of $\geqslant 50\%$ from the baseline or preexcision value at 10 min after gland excision is generally accepted as the criterion by which the surgeon could conclude that all abnormal glands had been removed, without having to identify all four glands (Figure 5). In a series of more than 600 cases performed by the traditional four-gland approach or by a minimally invasive procedure, the rates for double adenomas and hyperplasia were 11 and 7%, respectively, for the former approach and 5.1 and 1.6%, respectively, for the latter.[31] These findings underscore the fact that a subset of patients had enlarged glands that were not identified by sestamibi, ultrasound or IOPTH, but which would have been discovered with the traditional four-gland approach. The question remains as to whether enlarged glands that are not hypersecreting at the time of initial surgery will cause recurrent hyperparathyroidism in the future. The 6-month follow-up studies from the University of Miami have shown a cure rate of 98% with a focused approach.[32] In some series, a false-positive drop of PTH of $>50\%$ has been noted in 2–3% of patients, whereas a similar proportion of patients have had a false-negative drop in PTH at 10 min.[33,34]

Occasional normocalcemic patients may have increased levels of PTH at 1–5 years after apparent curative surgery.[35] At present, there is no evidence that postoperative increases in PTH levels are indicative of surgical failure. Potential mechanisms of PTH elevation in the setting of normocalcemia include vitamin D deficiency, hungry bone syndrome and PTH resistance.

Parathyroid carcinoma

Parathyroid carcinoma (PT-CA) is a rare tumor, which accounts for $<1\%$ of cases of P-HPT in most large series.[36] However, there is considerable variation in the incidence of this tumor in different parts of the world, with rates as high as 5% in some series.[37] Although this variability may represent true geographic differences, an alternative explanation may be related to differences in pathological criteria for the diagnosis of these tumors. There is little information on the etiology of PT-CA, but prior radiation does not seem to be a significant factor. Rare cases of PT-CA have been reported in patients with long-standing secondary hyperparathyroidism

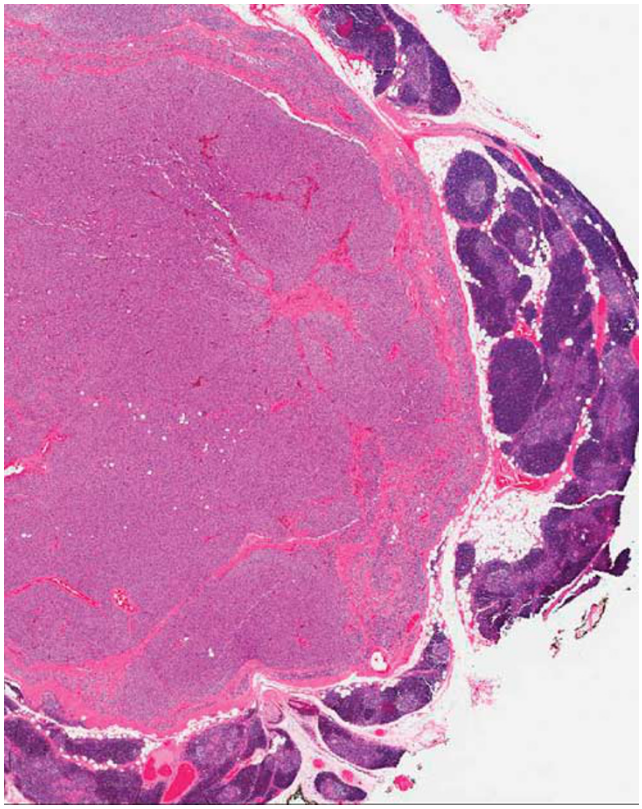

Figure 9 Intrathymic parathyroid adenoma. This noninvasive tumor has areas of fibrous banding.

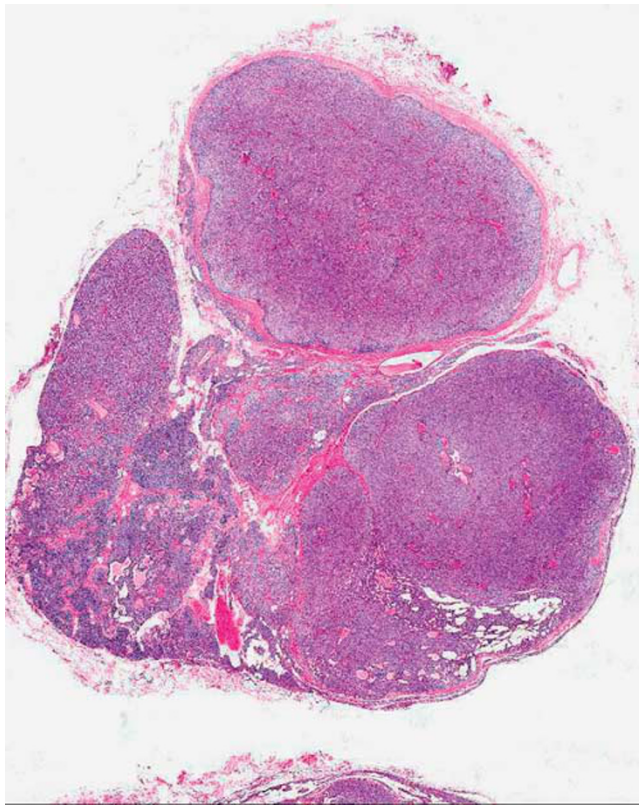

Figure 10 Multinodular parathyroid hyperplasia from a patient with MEN1.

(S-HPT).[38] Among heritable cases of hyperparathyroidism, PT-CA has been reported in ~15% of patients with the HPT-JT syndrome[39] (Table 1). An increased risk of PT-CA has also been reported in patients with familial isolated hyperparathyroidism.[40] PT-CA occurs rarely in MEN1[41] and a single case has been reported in a patient with type 2A MEN (MEN2A).[42]

In contrast to the 3–4:1 predominance of parathyroid adenomas in women, PT-CA has a roughly equal male to female sex ratio.[36] Moreover, PT-CA tends to occur ~10 years earlier than parathyroid adenoma. Generally, serum calcium values and PTH levels are higher in patients with carcinomas than adenomas, and patients with PT-CA are more likely to have palpable cervical masses and concomitant bone and kidney disease. Less than 10% of PT-CAs are nonfunctional.[43]

The pathological diagnosis of PT-CA is challenging with considerable interobserver diagnostic variability. In some series, a significant proportion of cases that recur and/or metastasize are classified as benign at first presentation.[44] On the other hand, only a small proportion of cases classified initially as PT-CA behave as true malignancies.[45] Whether the latter cases represent carcinomas cured by simple excision is unknown.

Parathyroid carcinomas are typically larger than adenomas and are often adherent to the surrounding soft tissues or thyroid gland[37,46,47] (Figures 6 and 7). The diagnosis of malignancy should be restricted to those tumors with evidence of invasive growth involving adjacent structures, including the thyroid and soft tissues, (Figure 6b) blood vessels (Figure 6c) or perineural spaces (Figure 6d), or to those tumors with documented metastases (Figure 8a and b). Fibrous band formation, although common in carcinomas (Figure 6a), is insufficient for the diagnosis of malignancy as fibrosis also occurs in adenomas, particularly those of large size or with cystic change. Similarly, mitotic activity is common in PT-CAs (Figure 7a and b) and is also relatively common in adenomas; however, atypical mitoses usually indicate the presence of malignancy (Figure 7b). As noted by Bondeson *et al*,[48] the frequency of mitoses in PT-CAs did not exceed the values in benign parathyroid tumors. However, a substantial proportion of carcinomas in Bondeson's series had a markedly higher mitotic rate that was prognostically significant with respect to tumor aggressiveness. Analysis of proliferative fractions with Ki-67 has shown higher values in PT-CAs (6–8.4%) than in adenomas (2–3.3%), but the overlap in equivocal cases has limited the usefulness of this approach.[17–19] As compared with adenomas, carcinomas have a three- to fourfold decrease in p27 expression. These findings have suggested that low p27 and high Ki-67 scores may be useful in the discrimination of adenomas and carcinomas.[19]

Most carcinomas have a solid growth pattern with tumor cells arranged in cohesive cell masses (Figures 7a and b), whereas others have a nesting or trabecular growth pattern. Foci of necrosis may be present (Figure 7c). Bondeson *et al*[48] noted areas of coagulative necrosis in approximately one-third of carcinomas. However, necrosis may also be present in adenomas, particularly those of large size. There is considerable variation in the cytological composition of PT-CAs. In the series of cases reported by Bondeson *et al*,[48] 50% of the cases consisted almost entirely of chief cells, whereas oncocytes predominated in 11%. Eighteen percent had an admixture of chief cells and oncocytes, whereas a few tumors were composed of water-clear cells. The remaining tumors were composed of transitional oncocytes or vacuolated chief cells. There is generally mild-to-moderate nuclear atypia, but some tumors may be cytologically indistinguishable from adenomas (Figures 7a, 8a and b). Data from the National Cancer Database indicate that nearly 90% of PT-CAs are well or moderately differentiated.[49] In Bondeson *et al*[48] series, approximately two-thirds of the carcinomas exhibited cytological atypia. However, a subset of PT-CAs may exhibit considerable nuclear pleomorphism with macronucleoli. In summary, the presence of scattered foci of coagulative necrosis in addition to macronucleoli and mitotic activity in excess of 5 per 50 high-power microscopic fields constitutes a triad indicative of a high risk of malignant behavior[48] (Figure 7b and c). The most common metastatic sites include cervical lymph nodes, lung (Figure 8a and b) and liver.

Several groups have shown LOH on chromosome 13q, a region that includes both *RB* and *BRCA2* in PT-CAs. Cryns *et al*[50] reported that 11 of 11 specimens from patients with these tumors lacked an RB allele, whereas only 1 of 19 adenomas lacked an RB allele. Correlative immunohistochemical studies showed a complete or predominant absence of RB in carcinomas, whereas none of the adenomas had abnormal staining patterns. However, subsequent immunohistochemical studies have failed to confirm these observations.[51] The contribution of *RB* and *BRCA2* to the development of parathyroid malignancies has been controversial. In a recent study, LOH for at least one marker of the *RB* allele was found in 6 of 6 carcinomas, whereas LOH for *BRAC2* was found in 3 of 5 cases.[52] In the same series, LOH of *RB* and *BRCA2* was shown in 28.8% and 17.4% of adenomas, respectively. Direct sequencing studies of carcinomas that showed LOH of *RB* or *BRCA2* were negative for microdeletions, insertions or point mutations of either gene.[53] These workers concluded that neither *RB* nor *BRCA2* were likely to act as tumor suppressor genes in carcinomas. However, these results do not exclude the possibility that decreased *RB* function in carcinomas, whether secondary or occurring as a result of epigenetic effects, may have a role in tumor development.

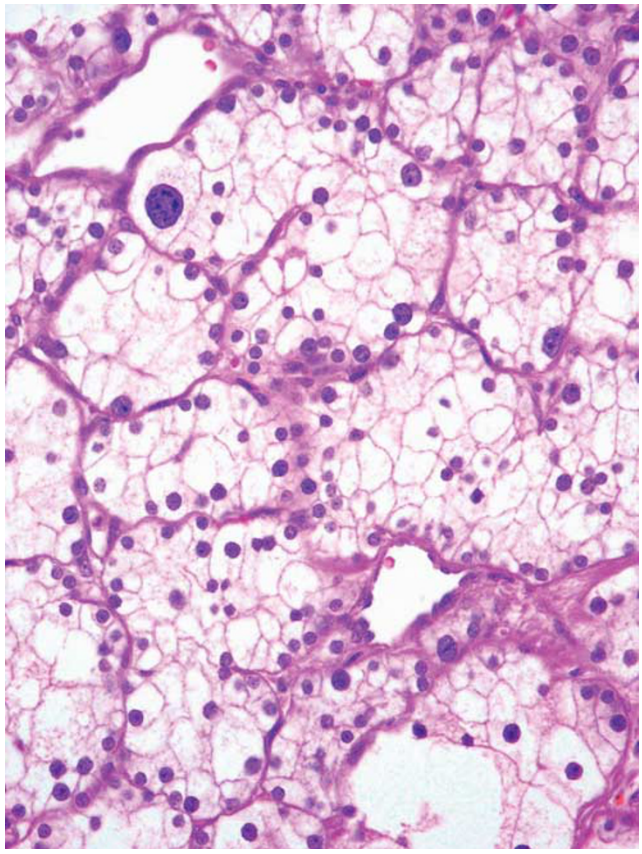

Figure 11 Water-clear hyperplasia. The cells have abundant vacuolated cytoplasm with occasional enlarged and hyperchromatic nuclei.

The HPT-JT syndrome is a rare autosomal dominant syndrome characterized by hyperparathyroidism and fibro-osseous lesions of the mandible and maxilla. Affected patients may also have evidence of a variety of renal lesions including cysts, hamartomas, renal cell carcinoma and Wilms' tumors.[39,54] Hyperparathyroidism is due to the presence of multiple adenomas, some of which are cystic. Approximately 10–15% of affected patients have PT-CA. Mutations of the *HRPT2* gene (1q25-q32), which encodes parafibromin, are responsible for the development of the syndrome.[55]

The *HRPT2* gene (1q25-q32) was first implicated in the development of sporadic PT-CAs in 2003.[56,57] These mutations were predicted to inactivate the parafibromin protein. Shattuck *et al* further showed that a subset of patients who were positive for somatic mutation of this gene were also positive for a germline mutation of the same gene. This finding suggested that a subset of patients with apparent sporadic PT-CAs carried germline mutations of the *HRPT2* gene and might have the HPT-JT syndrome or a *forme fruste* of the syndrome. Patients with PT-CA, therefore, should have jaw and kidney imaging studies. If the HPT-JT syndrome is diagnosed, family members should undergo molecular testing and imaging studies.

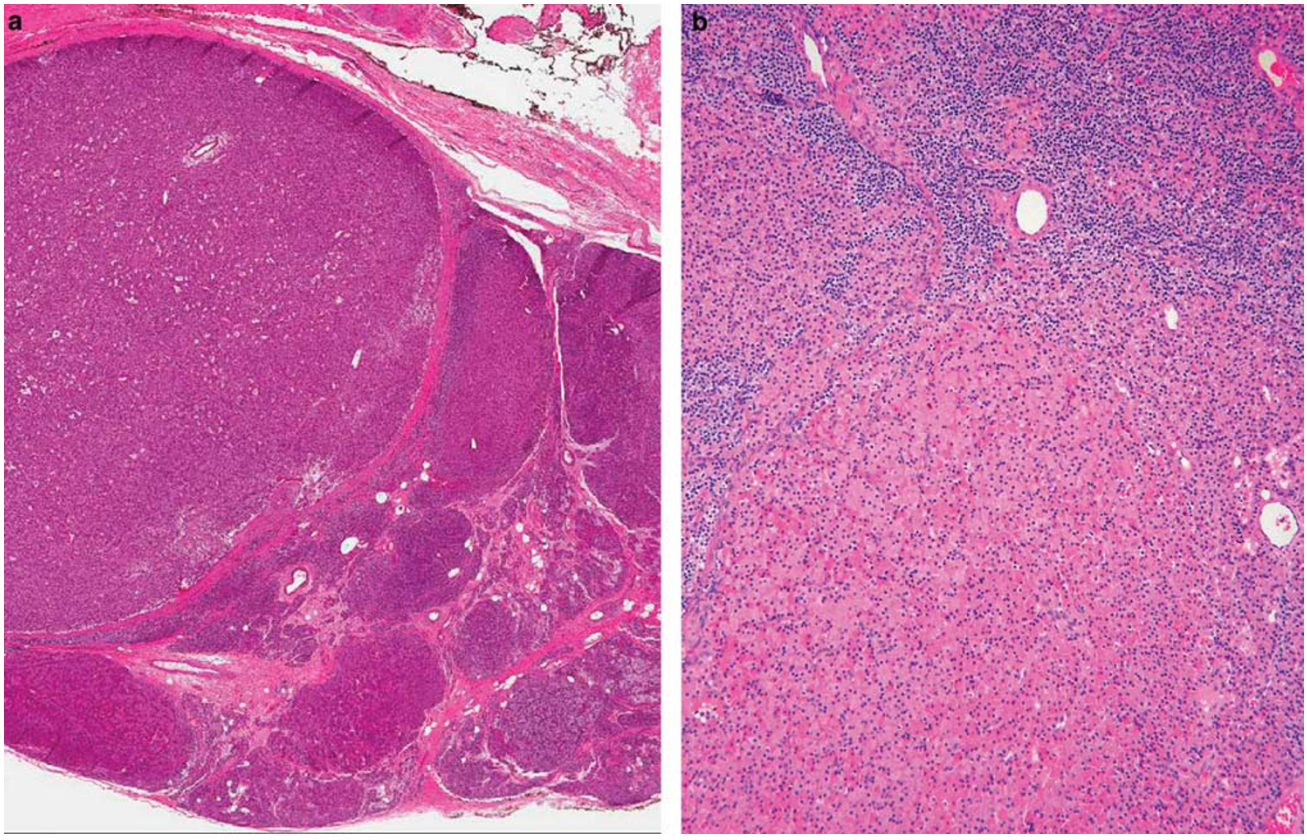

Figure 12 (**a**) Secondary parathyroid hyperplasia. This gland has a multinodular appearance. The largest nodule is surrounded by a fibrous capsule. (**b**) Secondary parathyroid hyperplasia. This field contains an oncocytic nodule.

Loss of parafibromin expression was reported as a marker for PT-CA by Tan *et al*[58] These workers noted that loss of parafibromin nuclear immunoreactivity had a 96% sensitivity and a 99% sensitivity for the diagnosis of this tumor. Parathyroid adenomas associated with the HPT-JT syndrome have also been negative. Similar results have been reported by other workers.[59,60] However, in our own experience, loss of parafibromin staining has been observed in some adenomas unassociated with the HPT-JT syndrome, whereas some PT-CAs have been positive.[61] On the basis of a detailed literature review, 46% of PT-CAs have been reported as parafibromin negative, whereas 88% of cases have been reported as negative and/or weakly positive. Some of the differences in the frequency of negativity are undoubtedly related to case selection criteria, differences in primary antibodies and retrieval methods and differing criteria for the assessment of reactivity patterns. Interestingly, parafibromin has been shown in metastatic PT-CAs in patients with renal failure.[62] Despite these reservations, lack of parafibromin staining offers promise as a marker of parathyroid malignancy.[63] Additional markers for the diagnosis of PT-CA include galectin-3 (↑ expression),[64] PGP 9.5 (↑ expression)[65] and APC (loss);[66] however, the utility of these markers requires additional investigation.

Atypical adenoma

Atypical adenomas of the parathyroid gland are a controversial entity.[67] Although these tumors have some of the features of carcinomas (banding fibrosis, mitotic activity, trabecular growth, adherence of tumor to adjacent soft tissues or thyroid and entrapment of lesional cells into the surrounding capsule), they lack unequivocal evidence of invasive growth[68,69] (Figure 9). Patients with atypical adenomas generally present with calcium levels intermediate between those of adenomas and carcinomas.[68,69] On the basis of studies reported in the literature and our own observations, atypical adenomas pursue a benign clinical course.[68] The molecular phenotype of atypical adenomas is intermediate between that of adenomas and carcinomas. Stojadinovic *et al.*[70] reported that the phenotype p27 (+), bcl2 (+), Ki-67 (−) and mdm (+) was present in 76% and 29% of typical adenomas and atypical adenomas, respectively, and in no cases of carcinoma. However, other workers have failed to confirm some of these observations.[71]

Chief cell hyperplasia

Primary chief cell hyperplasia represents an absolute increase in parathyroid parenchymal cell mass

involving multiple parathyroid glands in the absence of a known stimulus for PTH hypersecretion.[72] This disorder was first recognized by Cope *et al*[73] in 1958. Primary chief cell hyperplasia occurs sporadically in 75% of cases, whereas 25% of cases are heritable.[74] The proportion of heritable cases is likely to increase with the use of molecular diagnostic approaches for classification of hyperparathyroid states. The predominant cell type, as the name implies, is the chief cell, although variable numbers of oncocytes and transitional oncocytes are observed. The glands are increased in weight and have an increased ratio of parenchymal cells to fat. The enlargement of the glands is symmetric in ~50% of the cases and is asymmetric in the remainder. Although some cases of chief cell hyperplasia have a diffuse pattern of growth, other cases of hyperplasia, particularly in those occurring in MEN1, are nodular and may have a rim of normocellular parathyroid tissue at their peripheries (Figure 10). Heritable forms of HPT include MEN1,[75] MEN2,[76] familial hypocalciuric hypercalcemia (FHH),[74] neonatal severe hyperparathyroidism,[74] the HPT-JT syndrome,[39,54] familial isolated hyperparathyroidism (FIHPT)[77] and familial hypercalcemic hypercalcuria[78] (Table 1).

The MEN1 syndrome is inherited as a autosomal dominant trait that is characterized by the development of multifocal parathyroid tumors (90% of cases), gastroenteropancreatic neuroendocrine tumors, pituitary adenomas and a variety of other tumors.[75] This syndrome occurs as a result of germline mutations that are spread over the entire coding and intronic regions of the MEN1 gene, with more than 400 different recognized sites. The development of parathyroid and other tumors in the syndrome occurs as a result of inactivation of the wild-type allele at the somatic level. Although the parathyroid disease has been classified as hyperplasia, the individual parathyroid lesions represent clonal proliferations that are more closely related to adenomas.[21,79,80] For this reason, it may be preferable to refer to these cases as 'multiglandular parathyroid disease' rather than hyperplasia. Similar results have been reported by Arnold *et al*[81] in a series of 16 patients with nonfamilial primary chief cell hyperplasia.

Multiple endocrine neoplasia 2A is an autosomal dominant trait characterized by the development of C-cell hyperplasia and medullary thyroid carcinoma, pheochromocytomas and chief cell hyperplasia (20–30% of cases).[76] Dominant activating mutations of the *RET* oncogene (10q11.2) are responsible for the development of MEN2A, MEN2B and isolated familial medullary thyroid carcinoma. Parathyroid abnormalities do not occur in the MEN2B syndrome.

Familial hypocalciuric hypercalcemia is an autosomal dominant trait and occurs most frequently as a result of loss of function mutations of the *CaSR* gene on 3q 21.1.[74] Neonatal severe hyperparathyroidism represents the homozygous form of FHH. Familial isolated hyperparathyroidism is characterized by chief cell hyperplasia and has been associated with mutations of *MEN1*, *CaSR* and *HRPT2*.[77] Familial hypercalcemic hypercalciuria/autosomal dominant mild hyperparathyroidism is an exceptionally rare disorder due to an inactivating mutation in the *CaSR* gene.[78]

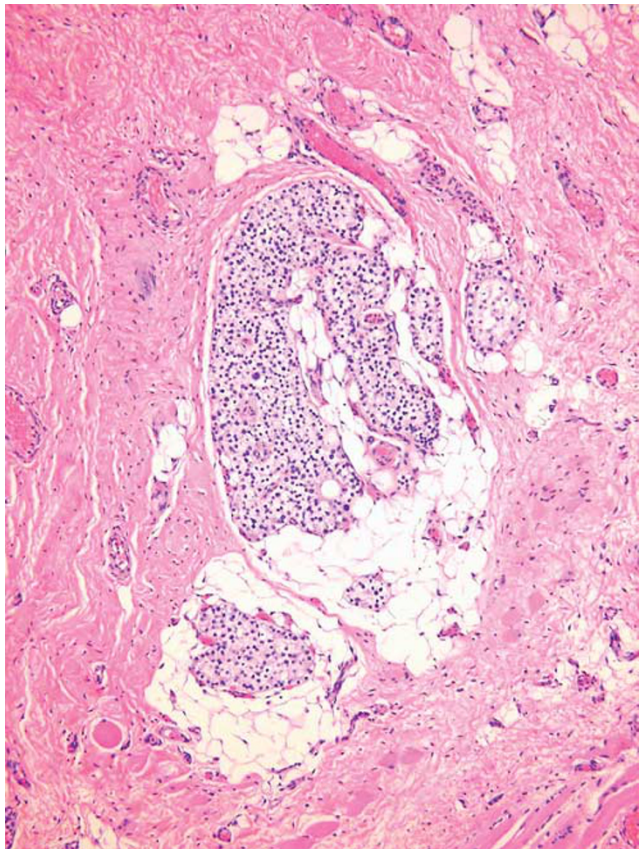

Figure 13 Parathyromatosis. This patient with primary chief cell hyperplasia developed recurrent hyperparathyroidism after subtotal parathyroidectomy. Multiple foci of parathyroid chief cells surrounded by areas of fibrosis were present in the cervical soft tissue after re-exploration.

Primary water-clear cell hyperplasia

Primary water-clear cell hyperplasia is a rare disorder that was first recognized in 1934 by Albright *et al*.[82] In contrast to chief cell hyperplasia, primary water-clear cell hyperplasia has no known association with the heritable hyperparathyroidism syndromes. The degree of hypercalcemia is generally greater than that seen in patients with chief cell hyperplasia. There is a considerable variation in the size and weight of the glands, with total glandular weights varying between 1 and 60 g. All four glands are usually involved, although the upper glands tend to be larger than the lower glands. Affected glands are frequently cystic and hemorrhagic. Microscopically, cytoplasmic clearing is due to the

presence of numerous small vacuoles that are derived from the Golgi apparatus[83] (Figure 11). The nuclei are generally round and regular with dense chromatin; however, occasional cells with enlarged and hyperchromatic nuclei may be evident. Kuhel *et al* reported a case of synchronous water-clear cell adenoma involving both upper parathyroid glands.[84] Despite the fact that the two lesions were clonal on the basis of molecular studies, the possibility that this case represented asymmetric hyperplasia could not be entirely ruled out.

Secondary and tertiary hyperparathyroidism

Secondary hyperparathyroidism represents an adaptive increase in the synthesis and secretion of PTH that results from hypocalcemia of diverse etiologies, including chronic renal failure, vitamin D deficiency and intestinal malabsorption states.[72] Tertiary hyperparathyroidism refers to the development of autonomous parathyroid hyperfunction patients with preexisting S-HPT. Pathologically, these disorders are associated with increased glandular weight and cellularity. Patients with S-HPT generally have greater uniformity in gland size than patients with P-HPT, particularly in the early stages of this disease. With further progression the glands often assume a multinodular configuration with areas of hemorrhage, cyst formation, fibrosis and chronic inflammation (Figure 12a). As a result, the distinction of such cases from PT-CA is sometimes difficult. The presence of multiglandular disease, the absence of vascular invasion and the appropriate clinical history are all helpful in making this distinction. Chief cells predominate in early phases of the disease, whereas oncocytes often represent the dominant cell population in advanced cases (Figure 12b). In all probability, the earliest phases of secondary hyperplasia are polyclonal lesions. A large majority of patients with chronic renal failure who require surgery have clonal parathyroid lesions.[81] Interestingly, histopathological categories of nodular versus diffuse hyperplasia are not useful predictors of clonal status.

Parathyromatosis

Developmental rests of parathyroid tissue are relatively common in the soft tissues of the mediastinum and neck, often in proximity to normal parathyroid glands. In patients with primary or secondary parathyroid hyperplasia, the rests may also become hyperplastic, a phenomenon that has been termed 'parathyromatosis'.[85] Hyperplastic rests may be responsible for persistent or recurrent hypercalcemia after parathyroidectomy[86] (Figure 13). A second mechanism for the development of parathyromatosis is seeding of the operative field during parathyroidectomy or incomplete excision of a hyperplastic or adenomatous parathyroid gland.[86]

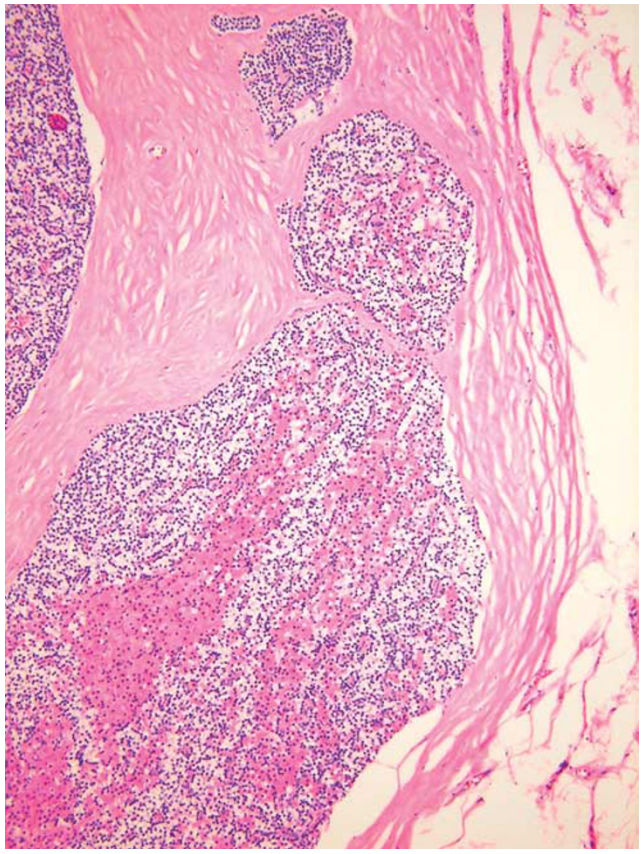

Figure 14 Hyperplastic parathyroid tissue after autotransplantation of parathyroid tissue in the forearm of a patient with secondary hyperparathyroidism treated by total parathyroidectomy. Nodules of chief cells and oncocytes surrounded by fibrous bands were present in the subcutaneous tissue.

The distinction of parathyromatosis from PT-CA is challenging. In patients with previously untreated primary or secondary hyperplasia, foci of parathyromatosis are unassociated with desmoplasia. However, in patients with previous surgery, parathyromatosis may be associated with considerable fibrosis, invasion of skeletal muscle and soft tissues and mitotic activity, features that are similar to parathyroid autotransplants (Figure 14). Vascular invasion, on the other hand, is absent. Recent studies indicate that the molecular profiles of parathyromatosis are similar to those of benign parathyroid tumors with respect to expression of parafibromin, Ki-67, RB and galectin-3.[71]

Disclosure/conflict of interest

The author declares no conflict of interest.

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