Hyperparathyroid Disorders

3

Qaisar Hussain Siraj

3.1 Introduction

Parathyroid disorders can result in either excessive production of parathyroid hormone causing hyperparathyroidism or underproduction of the hormone resulting in a hypoparathyroid state. This chapter deals with hyperparathyroid disorders, resulting from an overproduction of parathyroid hormone (PTH) with grave consequences to the patient's state of health. PTH is responsible for minute-to-minute regulation of serum calcium, and therefore parathyroid disorders, causing overproduction of PTH, profoundly affect serum calcium levels causing hypercalcaemia, which is defined as total serum calcium greater than 2 standard deviations above the normal mean, when corrected for serum albumin levels. Typically, this means a calcium level greater than 2.6 mmol/L. Hypercalcaemia as a result of hyperparathyroidism is a multisystem disease affecting the skeletal, renal, cardiovascular, gastrointestinal, and neuromuscular systems.

3.2 Symptoms and Signs of Hypercalcaemia

The historical adage 'moans, bones, groans and renal stones' have long been used to describe the symptoms of hypercalcaemia or hyperparathyroidism, but these are not specific to either diagnosis alone and represent a combination of both [1]. Table 3.1 lists the gamut of symptoms associated with hypercalcaemia due to hyperparathyroidism.

These classic symptoms have long been considered pathognomonic of the disease, but thanks to the automated laboratory biochemistry procedures, the diagnosis is now being made at an early stage in the disease, when most patients are yet

Q. H. Siraj (✉)
Department of Nuclear Medicine, Farwaniya Hospital, Kuwait

Q. Siraj (ed.), *Radionuclide Parathyroid Imaging*,
https://doi.org/10.1007/978-3-030-17351-7_3

Table 3.1 Symptoms and signs of hypercalcaemia

Gastrointestinal symptoms (moans):
Abdominal pain
Anorexia
Nausea, vomiting
Vomiting
Constipation
Peptic ulceration
Pancreatitis (rare)
Neuromuscular (groans):
Muscle weakness
Fatigue
Headache
Depression
Mental instability
Lethargy
Confusion
Psychotic behaviour
Stupor
Coma
Skeletal (bones):
Bone pain
Arthralgia
Osteitis fibrosa cystica (von Recklinghausen's disease of the bone)
Osteoporosis
Renal (renal stones):
Polyuria (nocturia)
Polydipsia
Nephrocalcinosis
Nephrolithiasis
Nephrogenic diabetes insipidus
Renal failure
Cardiovascular:
Arrhythmias
Bradycardia
Short QT interval
Bundle branch block
Atrioventricular block
Hypertension (rare)
Cardiac arrest (rare)
Venous thrombosis
Vascular calcification

asymptomatic. Biochemical hypercalcaemia and hyperparathyroidism are diagnostic, but increasingly, normal or borderline sporadic elevations in serum calcium with inappropriate PTH elevation are the only clue to what is now termed as eucalcaemic or normocalcaemic hyperparathyroidism [2]. This coupled with widespread vitamin D deficiency, which results in an increase in the PTH in the presence of normal serum calcium, makes the diagnosis somewhat confounding.

The severity of symptoms is related not only to the absolute calcium level but also to the rate of the rise in serum calcium levels. Patients with mild hypercalcaemia (serum calcium level <2.75 mmol/L) are mostly asymptomatic though some may report mild fatigue, vague changes in cognitive function, depression, or constipation.

Patients with moderate hypercalcaemia (serum calcium level 3.0–3.50 mmol/L) more commonly report the typical hypercalcaemic symptoms such as anorexia, nausea, abdominal pain, muscle weakness, and mental depression. Polyuria and polydipsia are common as a result of dehydration associated with a decreased urinary concentration ability secondary to hypercalcaemia. Patients with calcium levels >3.50 mmol/L may have progressive lethargy, disorientation, and even coma. Elderly or debilitated patients are more likely to be symptomatic even with mild hypercalcaemia. However, patients with chronic hypercalcaemia, despite higher serum calcium values (at around 3.75–4.0 mmol/L), are likely to have fewer symptoms compared with those showing an acute rise in the serum calcium level [3].

3.3 Causes of Hypercalcaemia

The causes of hypercalcaemia can be classified into two major categories: (1) non-PTH-related (Table 3.2) and (2) PTH-related (Table 3.3).

Table 3.2 PTH-independent causes of hypercalcaemia

Humoral hypercalcaemia of malignancy (HHM): PTHrP-mediated
Squamous carcinoma of the lung, oropharynx, nasopharynx, larynx, and oesophagus
Gynaecologic (cervical and ovarian)
Urologic (renal, transitional cell of the bladder)
Pheochromocytoma
Pancreatic islet cell tumours
T-cell lymphoma
Others
HHM: excess calcitriol (1,25-(OH)2-D3) mediated
B-cell lymphoma
Local osteolytic hypercalcaemia
Multiple myeloma
Breast carcinoma metastatic to bone
Lymphoma
Others
Medications/supplements
Vitamins A and D
Calcium-containing antacids (milk-alkali syndrome)
Thiazide diuretics
Granulomatous diseases
Sarcoidosis
Tuberculosis
Histoplasmosis
Leprosy
Endocrine
Severe thyrotoxicosis
Adrenal insufficiency
Pheochromocytoma
Other conditions
Factitious hypercalcaemia (due to increased plasma protein levels)
Acute renal failure
Immobilisation
Post rhabdomyolysis

Table 3.3 Causes of hypercalcaemia secondary to hyperparathyroidism (PTH-dependent hypercalcaemia)

Primary hyperparathyroidism (sporadic)
Tertiary hyperparathyroidism
Hereditary
Familial isolated
MEN 1
MEN 2A
MEN 4
HPT-JT
CaSR disorders
Familial hypocalciuric hypercalcaemia
Neonatal severe hyperparathyroidism
Ectopic PTH production
Lithium

Hypercalcaemia of malignancy has two forms: humoral hypercalcaemia of malignancy (HHM) and local osteolytic hypercalcaemia (LOH). The PTH-related protein (PTHrP) action accounts for the majority of HHM, whereas LOH results from the release of cytokines or other factors that activate bone resorption by osteoclasts from tumours growing in the bone. The amino terminus of the PTHrP peptide is homologous with PTH, and they share a common receptor. The metabolic effects of PTHrP are similar to those of PTH including activation of osteoclasts to resorb bone, decreasing renal calcium loss, and increasing renal phosphate clearance [4].

PTH-independent hypercalcaemia may occur due to excess production of calcitriol by granulomas, or bone resorption in severe hyperthyroidism or immobilised patients, or volume depletion in Addison's disease, or excessive intake of vitamins A and D causing bone resorption, or enhanced renal calcium reabsorption caused by thiazide diuretics.

Clinically, on the basis of the cause of hypersecretion of the PTH, hyperparathyroidism can be divided into primary, secondary, and tertiary types. Primary hyperparathyroidism (PHPT) is characterised by hypercalcaemia due to inappropriate secretion of PTH from one or more parathyroid glands in the absence of a known stimulus to parathyroid enlargement [5, 6].

Secondary hyperparathyroidism (SHPT), also known as renal osteodystrophy, is compensatory functional hyperplasia and hypertrophy of the parathyroid glands due to chronic kidney disease and is caused by hypocalcaemia or vitamin D deficiency, or both, or due to peripheral resistance to parathyroid hormone. The condition is usually associated with multiglandular parathyroid hyperplasia, although parathyroid adenomas may develop in rare instances.

The most common underlying cause of SHPT is end-stage renal failure, with vitamin D deficiency and malabsorption syndromes being less common causes. Less commonly, SHPT may be caused by calcium malabsorption, osteomalacia, vitamin D deficiency, or deranged vitamin D metabolism. It is typically associated with low or normal concentrations of serum calcium and increased PTH secretion, which represents an adaptive response, most commonly in patients with hypocalcaemia or hyperphosphataemia associated with renal failure [7]. The conversion of

25(OH)D to 1,25(OH)2D is also impaired, leading to decreased intestinal calcium absorption. In contrast to primary hyperparathyroidism, treating the underlying cause can reverse secondary hyperparathyroidism.

In PHPT, oversecretion of PTH results in impaired renal function due to hypercalcaemia caused by increased calcium absorption from the gut and calcium mobilisation from the bone. Sustained and non-treated PHPT results in renal failure with SHPT as a sequel, and hence it might be difficult to distinguish between PHPT and SHPT in the presence of renal injury.

Tertiary hyperparathyroidism refers to autonomous parathyroid hyperfunction in patients who have a history of prior secondary hyperparathyroidism in which the glandular hyperfunction and hypersecretion continue despite correction of the underlying abnormality, as in renal transplantation [8].

Familial hypocalciuric hypercalcaemia (FHH) is a genetic disorder due to calcium-sensing receptor (CaSR) mutation resulting in impaired inhibition of calcium reabsorption in the renal proximal convoluted tubule thick ascending limb of loop of Henle causing hypercalcaemia in the presence of an inappropriately normal PTH [9].

Lithium therapy can change the set point for the CaSR on the parathyroid gland so that a higher serum calcium concentration is needed to inhibit PTH secretion.

Rare cases of ectopic PTH-secreting tumours (small cell lung cancers, ovarian cancers, and papillary thyroid cancer) causing hypercalcaemia and hyperparathyroidism in the absence of a parathyroid adenoma have been reported [10, 11].

3.4 Primary Hyperparathyroidism (PHPT)

Primary hyperparathyroidism (PHPT) is an endocrine disorder that develops as a result of autonomous production and secretion of parathyroid hormone (PTH) from parathyroid gland (s). It is the most common cause of hypercalcaemia with an incidence of about 3:1000 in the general population though it is thought to be rising as a result of the introduction of automated methods for serum calcium determination. It is defined by an elevation of ionised serum calcium in the setting of an inappropriate elevation of PTH [12]. The diagnosis may extend from normocalcaemia accompanied by elevated PTH levels to hypercalcaemia accompanied by elevated or inappropriately normal PTH levels. The disorder results from abnormal hypersecretion of parathyroid hormone in the face of persistent hypercalcaemia due to a disorder of negative feedback inhibition of the parathyroid glands. PHPT is the most common cause of PTH and calcium level elevation and the third most common endocrine disorder, after diabetes and thyroid dysfunction. PHPT is either hereditary or sporadic.

3.4.1 Hereditary PHPT

Primary hyperparathyroidism (PHPT) is usually a sporadic disease, but in approximately 5–10% of cases, a familial and hereditary hyperparathyroid syndrome is

diagnosed. The familial causes include familial isolated hyperparathyroidism, MEN 1, MEN 2A, MEN 4, and hyperparathyroidism-jaw tumour (HPT-JT) syndrome.

Familial isolated hyperparathyroidism is an inherited form of primary hyperparathyroidism characterised by parathyroid adenoma/hyperplasia in the absence of other associated endocrinopathies. In some cases, individuals also develop parathyroid carcinoma.

Multiple endocrine neoplasia (MEN) syndromes are a group of hereditary syndromes with an autosomal dominant hereditary pattern with a predilection to develop tumours of the endocrine organs, including the parathyroid glands. MEN syndromes are characterised by neoplasms in two or more endocrine organs. The neoplasms can be benign or malignant and secretory or non-secretory. Syndromes, in which primary hyperparathyroidism has been described, include MEN 1, MEN 2, and MEN 4 [13]. MEN 1 and MEN 2 are neoplastic syndromes which demonstrate an autosomal dominant inheritance pattern.

In MEN 1 syndrome, PHPT is the earliest and the most frequent expression with 80% occurrence, reaching 90% by the age of 35 years and almost 100% by the age of 50 years [14, 15].

Pancreatic endocrine tumours, anterior pituitary gland neoplasms and PHPT characterise MEN 1. The cause of PHPT in MEN 1 is hyperplasia of all four parathyroid glands over the lifetime of the patient, and there is an increased incidence of supernumerary glands by up to 20%, which are ectopically located [16].

MEN 2A is defined by medullary thyroid carcinoma, pheochromocytoma in about 50% of the patients, and PHPT caused by parathyroid gland hyperplasia in about 20% of patients. Clinical expression of MEN 1 and MEN 2A is different from sporadic hyperparathyroidism and is summed in Table 3.4 [17].

MEN 4 is a newly identified MEN syndrome with phenotypic overlap of both MEN 1 and MEN 2. It consists of bilateral pheochromocytomas, parathyroid adenomas, multifocal thyroid C-cell hyperplasia, paragangliomas, and endocrine pancreatic hyperplasia [18].

HPT-JT syndrome is a rare but unique autosomal dominant form of familial hyperparathyroidism syndrome, characterised by hyperparathyroidism due to multiple adenomas, and mandibular or maxillary ossifying fibromas, with a significantly increased prevalence of carcinomas and atypical adenomas, uterine tumours, and cystic and neoplastic renal lesions [19, 20].

Table 3.4 Expression of primary hyperparathyroidism by syndrome

Feature	Sporadic hyperparathyroidism	MEN 1	MEN 2A
Inheritance	None	Autosomal dominant	Autosomal dominant
Mean age of onset	55 years	25 years	>30 years
M:F ratio	1:3	1:1	1:1
Multiplicity	Single ~80% of cases	Multiple	Can be multiple
Other common tumours	None	Pancreatic tumours Pituitary tumours	Medullary thyroid cancer Pheochromocytoma

3.4.2 Sporadic PHPT

In the majority of cases (~90%), PHPT is a sporadic, non-familial, and non-syndromic disease [21]. An isolated parathyroid adenoma causes the pathologic lesions responsible for sporadic PHPT in approximately 85% of cases, 15% by diffuse parathyroid hyperplasia, 1–4% by double parathyroid adenomas, and <1% by parathyroid carcinoma [22–25]. Parathyroid adenomas are benign monoclonal tumours resulting from the neoplastic proliferation of a single abnormal cell, which autonomously produces and secretes the parathyroid hormone. This parathyroid gland disorder can occur in all age groups though it is rare in children, with a peak incidence in the sixth decade of life, with a female-to-male ratio between 2 and 3:1 [5].

3.4.3 Parathyroid Adenoma

3.4.3.1 Solitary Adenoma

Parathyroid adenoma can originate in any of the four parathyroid glands but is more common in the lower glands [26]. Grossly, adenomas are oval- or kidney-shaped, reddish brown in colour, and soft in consistency [27]. Parathyroid adenomas can vary markedly in size and weight, with the gland size ranging from <1 to >3 cm and the weight ranging from 50 mg to several grams [6]. The normal glands in patients with a parathyroid adenoma are suppressed with lower secretory activity and are smaller in size.

The tumour cells are usually arranged in nests and cords surrounded by a rich capillary network. In the majority of parathyroid adenomas, the chief cells are the dominant cell type, with varying proportions of oxyphil and transitional oxyphil cells seen scattered within the collections of chief cells [28]. Chief cell adenomas have rounded, hyperchromatic, pleomorphic nuclei, which are larger than those present in the normal parathyroid tissue. The histological diagnosis of an adenoma and hyperplasia rests on finding a rim of intervening normal or suppressed parathyroid tissue.

Oxyphil cell or oncocytic adenomas occur less frequently and are found in the sixth to seventh decades of life. They tend to be larger than the chief cell adenomas and are either non-functional or associated with minimal elevation of serum calcium levels [29].

Water-clear cell parathyroid adenoma as a cause of PHPT is extremely rare with only few reported cases to date [30, 31]. These adenomas consist of nests and acini of water-clear cells containing abundant foamy, granular cytoplasm, and mild nuclear pleomorphism.

3.4.3.2 Double or Multiple Adenomas

Parathyroid adenomas are most commonly a single-gland disease, but rarely double-gland or multigland parathyroid adenomas have been reported [32]. ‘Double’ or ‘multiple’ adenomas in some cases might well represent asymmetric or asynchronous multigland hyperplasia [33]. Patients with double or multiple adenomas are

understandably relatively more symptomatic with higher PTH and serum alkaline phosphatase levels than those with solitary parathyroid adenomas or hyperplasia.

3.4.3.3 Microadenoma

Very rarely, tiny parathyroid adenomas can develop in parathyroid glands that are normal in size (6–7 mm) and weight (50–60 mg) [34]. Typical parathyroid adenomas are surrounded by a fibrous capsule; however, microadenomas (weighing <10 mg) are usually non-encapsulated [35].

3.4.3.4 Lipoadenomas

Lipoadenomas or parathyroid hamartomas are quite rare with an equal sexual predilection and occur beyond the fourth decade of life [36]. They consist of nests and cords of chief cells with a few intimately mixed oxyphil cells with a variable amount of mature adipose tissue and fibrous stroma. These may or may not be functional [33]. The high-fat content and relatively lower function make them difficult to diagnose on scintigraphy [36].

3.4.3.5 Cystic Adenoma (Functional Parathyroid Cyst)

Parathyroid adenomas with central necrosis or cystic degeneration are known as functional parathyroid cysts as opposed to the asymptomatic true parathyroid cysts which are embryonic vestiges or enlarged colloid microcysts within the parathyroids. They represent <9% of all adenomas and are frequently associated with PHPT [37, 38].

3.4.4 Parathyroid Hyperplasia

Parathyroid hyperplasia usually affects 10–15% of cases with sporadic PHPT. The multigland enlargement may be diffuse, asymmetric, or asynchronous. There are two major histological types of hyperplasia with the predominant majority of hyperplasia representing chief cell proliferation, although, very rarely, the water-clear cell hyperplasia can be encountered.

3.4.4.1 Chief Cell Hyperplasia

Chief cell hyperplasia, also known as nodular hyperplasia due to the range of cell types found, can occur in either primary or secondary hyperparathyroidism. Chief cell hyperplasia is commonly seen in PHPT associated with MEN 1 and MEN 2A syndromes. The hyperplastic glands are rounded and grossly lobulated, grey or brown in colour, and vary in weight from 50 mg to over 10 g. In chief cell hyperplasia associated with secondary hyperparathyroidism, the glands are hard, nodular, and firm, with the nodules macroscopically resembling multinodular thyroid disease [39]. Hyperplastic glands in patients with tertiary hyperparathyroidism are even larger in size and show more asymmetric enlargement and parenchymal nodularity.

3.4.4.2 Water-Clear Cell Hyperplasia

Water-clear cell hyperplasia is a very rare condition with marked enlargement of all four glands, which are lobulated, chocolate brown in colour, and translucent. The upper glands, however, can be 5–10 times larger than the lower pair of glands. The water-clear cell hyperplastic glands commonly contain large cysts with haemorrhagic areas. Histologically, the gland contains large (20 μm) water-clear cells with peripherally located nuclei [35, 39].

3.4.5 Parathyroid Carcinoma

Parathyroid carcinoma is very rare accounting for <1% to 5% of cases of sporadic PHPT [40, 41] with a challenging histological diagnosis. The World Health Organization histopathological criteria for parathyroid carcinoma diagnosis include unequivocal presence of vascular invasion in the capsule or adjacent tissues, perineural space invasion, capsular invasion with extension to adjacent tissues, and/or presence of metastases [42, 43].

Cancerous parathyroid glands generally weigh more than 1 g in weight, with the tumour appearing as a lobulated, firm, and encapsulated mass, which is generally larger than an adenoma in size [44]. Clinical and biochemical manifestations of parathyroid cancer are those of severe PHPT. The mean age at presentation is 50 years with equal preponderance between the two sexes [45, 46]. It is a slow-growing but eventually fatal cancer with 5-year survival ranging from 50% to 86% [46, 47]. Survival depends on the timely diagnosis, the pathological nature of the disease, and the surgical technique, but the primary determinant of survival is the uncontrollable hypercalcaemia and its fatal consequences [48].

References

1. Cox J, Stearns M. Symptoms, differential diagnosis and management. In: Arora A, Tolley N, Tuttle M, editors. A practical manual of thyroid and parathyroid disease. London: Wiley-Blackwell; 2010. p. 184–5.
2. Licata AA, Lerma EV, editors. Diseases of the parathyroid glands. Berlin: Springer Science+Business Media; 2012.
3. Holt EH. Diagnosis and treatment of the patient with abnormal calcium. In: Licata AA, Lerma EV, editors. Diseases of the parathyroid glands. Berlin: Springer Science+Business Media; 2012. https://doi.org/10.1007/978-1-4419-5550-0_3.
4. Dunbar ME, Wysolmerski JJ, Broadus AE. Parathyroid hormone-related protein: from hypercalcemia of malignancy to developmental regulatory molecule. Am J Med Sci. 1996;312:287.
5. DeLellis RA, Mazzaglia P, Mangray S. Primary hyperparathyroidism: a current perspective. Arch Pathol Lab Med. 2008;132:1251–62.
6. Carlson D. Parathyroid pathology: hyperparathyroidism and parathyroid tumors. Arch Pathol Lab Med. 2010;134:1639–44.
7. Rodriguez M, Canalejo A, Garfia B, Aguilera E, Almaden Y. Pathogenesis of refractory secondary hyperparathyroidism. Kidney Int. 2002;80:155–60.

8. Rivkees SA, el-Hajj-Fuleihan G, Brown EM, Crawford JD. Tertiary hyperparathyroidism during high phosphate therapy of familial hypophosphatemic rickets. J Clin Endocrinol Metab. 1992;75:1514–8.
9. Burski K, Torjussen B, Paulsen AQ, Boman H, Bollerslev J. Parathyroid adenoma in a subject with familial hypocalciuric hypercalcemia: coincidence or causality? J Clin Endocrinol Metab. 2002;87(3):1015–6.
10. Yoshimoto K, Yamasaki R, Sakai H, Tezuka U, Takahashi M, Iizuka M, Sekiya T, Saito S. Ectopic production of parathyroid hormone by small cell lung cancer in a patient with hypercalcemia. J Clin Endocrinol Metab. 1989;68(5):976–81.
11. Nussbaum SR, Gaz RD, Arnold A. Hypercalcemia and ectopic secretion of parathyroid hormone by an ovarian carcinoma with rearrangement of the gene for parathyroid hormone. N Engl J Med. 1990;323(19):1324–8.
12. Thompson NW, Eckhauser FE, Harness JK. The anatomy of primary hyperparathyroidism. Surgery. 1982;92:814–21.
13. Marx SJ. Molecular genetics of multiple endocrine neoplasia types 1 and 2. Nat Rev Cancer. 2005;5(5):367–75.
14. Tonelli F, Marcucci T, Giudici F, Falchetti A, Brandi ML. Surgical approach in hereditary hyperparathyroidism. Endocr J. 2009;56(7):827–41.
15. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJ, Lombardi G, Mannelli M, Pacini F, Ponder BA, Raue F, Skogseid B, Tamburrano G, Thakker RV, Thompson NW, Tomassetti P, Tonelli F, Wells SA Jr, Marx SJ. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658–71.
16. Lambert LA, Shapiro SE, Lee JE, Perrier ND, Truong M, Wallace MJ, Hoff AO, Gagel RF, Evans DB. Surgical treatment of hyperparathyroidism in patients with multiple endocrine neoplasia type 1. Arch Surg. 2005;140(4):374–82.
17. Zaidi SS, Lakhani VT, Broome JT. Hyperparathyroidism in multiple endocrine neoplasia. In: Licata AA, Lerma EV, editors. Diseases of the parathyroid glands. Berlin: Springer Science+Business Media, LLC; 2012. https://doi.org/10.1007/978-1-4419-5550-0_11.
18. Benson L, Ljunghall S, Akerstrom G, Oberg K. Hyperparathyroidism presenting as the first lesion in multiple endocrine neoplasia type 1. Am J Med. 1987;82(4):731–7.
19. Masi G, Barzon L, Iacobone M, Viel G, Porzionato A, Macchi V, De Caro R, Favia G, Palù G. Clinical, genetic, and histopathologic investigation of CDC73-related familial hyperparathyroidism. Endocr Relat Cancer. 2008;15:1115–26.
20. Iacobone M, Masi G, Barzon L, Porzionato A, Macchi V, Ciarleglio FA, Palù G, De Caro R, Viel G, Favia G. Hyperparathyroidism-jaw tumor syndrome: a report of three large kindred. Langenbecks Arch Surg. 2009;394:817–25.
21. Thakker RV. Genetics of parathyroid tumours. J Intern Med. 2016;280(6):574–83.
22. Massaro A, Cittadin S, Rampin L, et al. Accurate planning of minimally invasive surgery of parathyroid adenomas by means of [(99m)Tc]MIBI SPECT. Minerva Endocrinol. 2007;32:9–16.
23. Pelizzo MR, Piotto A, Bergamasco A, Rubello D. Parathyroid carcinoma. Therapeutic strategies derived from 20 years of experience. Minerva Endocrinol. 2001;26:23–9.
24. Lumachi F, Zucchetta P, Marzola MC, et al. Advantages of combined technetium-99m-sestamibi scintigraphy and high-resolution ultrasonography in parathyroid localization. Eur J Endocrinol. 2000;26:755–60.
25. Udelsman R. Primary hyperparathyroidism. In: Cameron JL, editor. Current surgical therapy. St. Louis, MO: Mosby; 2001. p. 662–7.
26. Grimelius L, Akerstrom G, Johansson H, Bergstrom R. Anatomy and histopathology of human parathyroid glands. Pathol Annu. 1981;16:1–24.
27. Summers GW. Parathyroid update: a review of 220 cases. Ear Nose Throat J. 1996;75:434–9.
28. Grimelius L, Johansson H. Pathology of parathyroid tumors. Semin Surg Oncol. 1997;13:142–54.

29. Giorgadze T, Stratton B, Baloch ZW, Livolsi VA. Oncocytic parathyroid adenoma: problem in cytological diagnosis. Diagn Cytopathol. 2004;31:276–80.
30. Bégueret H, Belleannée G, Dubrez J, Trouette H, Parrens M, Velly JF, de Mascarel A. Clear cell adenoma of the parathyroid gland: a rare and misleading lesion. Ann Pathol. 1999;19(4):316–9.
31. Prasad KK, Agarwal G, Krishnani N. Water-clear cell adenoma of the parathyroid gland: a rare entity. Indian J Pathol Microbiol. 2004;47(1):39–40.
32. Harkness JK, Ramsburg SR, Nishiyamarh RH, et al. Multiple adenomas of the parathyroids: do they exist? Arch Surg. 1979;114:468–74.
33. van der Walt J. Pathology of the parathyroid glands. Diagn Histopathol. 2012;18:221–33.
34. Liechly RD, Teter A, Suba EJ. The tiny parathyroid adenoma. Surgery. 1986;100:1048.
35. Mizamtsidi M, Nastos C, Mastorakos G, Dina R, Vassiliou I, Gazouli M, Palazzo F. Diagnosis, management, histology and genetics of sporadic primary hyperparathyroidism: old knowledge with new tricks. Endoc Connect. 2018;7(2):R56–68.
36. Turner WJD, Baergen RN, Pellitteri PK, Orloff LA. Parathyroid lipoadenoma: case report and review of the literature. Otolaryngol Head Neck Surg. 1996;114:313–6.
37. Rogers LA, Fetter BF, Peete WPJ. Parathyroid cyst and cystic degeneration of parathyroid adenoma. Arch Pathol. 1969;88:476–9.
38. Johnson NA, Yip L, Tublin ME. Cystic parathyroid adenoma: sonographic features and correlation with 99mTc-sestamibi SPECT findings. AJR Am J Roentgenol. 2010;195(6):1385–90. https://doi.org/10.2214/AJR.10.4472.
39. Lynn J, Lewis P. Pathological spectrum of parathyroid disease. In: Arora A, Tolley NS, Tuttle RM, editors. A practical manual of thyroid and parathyroid disease. Chichester: Wiley-Blackwell; 2010. p. 164–73.
40. Schantz A, Castleman B. Parathyroid carcinoma. A study of 70 cases. Cancer. 1973;31(3): 600–5.
41. Koea JB, Shaw JH. Parathyroid cancer: biology and management. Surg Oncol. 1999;8:155–65.
42. DeLellis RA. World health organisation classification of tumours. Pathology and genetics of tumours of endocrine organs. Lyon: AIRC; 2006.
43. Kruijff S, Sidhu SB, Sywak MS, Gill AJ, Delbridge LW. Negative parafibromin staining predicts malignant behavior in atypical parathyroid adenomas. Ann Surg Oncol. 2014;21:426–33.
44. Lack CA, Rarber JL, Rubin E. The endocrine system. In: Rubin E, Farber JL, editors. Pathology. 3rd ed. Philadelphia, PA: Lippincott-Raven; 1999. p. 1179–83.
45. Shane E. Clinical review 122: parathyroid carcinoma. J Clin Endocrinol Metab. 2001;86:485–93.
46. Hundahl SA, Fleming ID, Fremgen AM, et al. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985–1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1999;86:538–44.
47. Sandelin K, Auer G, Bondeson L, et al. Prognostic factors in parathyroid cancer: a review of 95 cases. World J Surg. 1992;16:724–31.
48. Kebebew E. Parathyroid carcinoma. Curr Treat Options Oncol. 2001;2:347–54.