[Frontiers in Bioscience S2, 299-312, January 1, 2010]

Parathyroid hormone-related peptide and primary hyperparathyroidism

Mario Testini[1], Angela Gurrado[1], Germana Lissidini[1], Giuseppe Piccinni[1], Luigi Greco[2], Francesco Basile[3], Antonio Biondi[3]

[1]Section of General Surgery, Department of Applications in Surgery of Innovative Technologies, University Medical School of Bari, Italy, [2]Section of General Surgery, Department of Emergency and Organ Transplantation, University Medical School of Bari, Italy, [3]Section of General Surgery and Oncology, Department of General Surgery, University Medical School of Catania, Italy

TABLE CONTENTS

1. ABSTRACT

The parathyroid hormone-related peptide (PTHrP) has been shown to be the major pathogenic factor to humoral hypercalcemia of malignancy (HHM). The presence of PTHrP in many normal tissues and in normal or abnormal parathyroids has been described in literature and its role has been investigated. PTHrP release from parathyroid cells into the extracellular space has been demonstrated to depend on the extracellular calcium concentration. The hormone binds to PTH type 1 Receptor (PTH1R) with a high affinity, as well as parathyroid hormone (PTH). These hormones' amino-terminal (1-34) peptide fragments are considered sufficient to achieve efficient receptor activation and action on mineral ion homeostasis. Generally, diagnosis of primary hyperparathyroidism (PHPT) is based on hypercalcaemia and elevated levels of PTH. The advent of intact-PTH immunoradiometric assay allowed us to distinguish PHPT from non-parathyroid-dependent hypercalcaemia, but the presentation of normal PTH level and hypercalcaemia due to a parathyroid adenoma is possible. The aim of the study is to identify the relationship between the production of PTHrP without malignancy and the diagnosis of PHPT by a systematic review.

2. INTRODUCTION

The parathyroid hormone-related peptide (PTHrP) has been shown to be the major pathogenic factor to humoral hypercalcemia of malignancy (HHM). However, the presence of PTHrP in many normal tissues has been described in literature and a role in normal physiology has been assumed (1).

Diagnosis of primary hyperparathyroidism (PHPT) is generally based on hypercalcaemia and high levels of parathyroid hormone (PTH); additional laboratory tests include hypophosphataemia and elevated urinary cyclic adenosine monophosphate (cAMP). The advent of the intact-PTH immunoradiometric assay has further increased the reliability of results, enabling PHPT to be distinguished from non-parathyroid-dependent hypercalcaemia. The presentation of a normal PTH level and hypercalcaemia due to a parathyroid adenoma is unusual; however, its incidence has been estimated to be between 5% and 33% (2-4).

PTHrP has been found in parathyroid tissue, but its role in causing hyperparathyroidism has not yet been defined (5).

The aim of the study is to identify the relationship between the production of PTHrP without malignancy and the diagnosis of PHPT by means of a systematic review according to recently presented guidelines on the argument. A comprehensive literature search was performed in December 2008 by consulting PubMed MEDLINE for publications and matching the terms of PTHrP and normal PTH level AND primary hyperparathyroidism/hypercalcaemia/parathyroid adenoma.

3. HYPERCALCAEMIA

Although the upper limit of normal can vary depending on the laboratory, hypercalcaemia is usually defined as a serum calcium level greater than 10.2 mg/dl, corrected for serum albumin concentration. Levels of higher than 14 mg/dl can be life threatening.

The clinical manifestations of hypercalcaemia will depend on the magnitude of this disorder. The most common symptoms are the nausea, vomiting, constipation and abdominal pain. Peptic ulcer disease and pancreatitis are rarely among the gastrointestinal manifestations. Furthermore, hypercalcaemia can determine difficulty in concentrating, corneal calcification, confusion and lethargy, fatigue and muscle weakness. Other effects are represented by vascular calcification, hypertension, shortening of the QT interval on the electrocardiogram and rare cardiac arrhythmias like digitalis toxicity. Significantly, hypercalcaemia can induce nephrolithiasis resulting from hypercalciuria, nephrogenic diabetes and, in the setting of volume depletion, acute renal failure.

However, diagnosis often is made incidentally in asymptomatic patients.The hypercalcaemia is one of the most common metabolic disorders and it could be generated by many different pathologic conditions. The most common categories are malignancy, PHPT and vitamin D-induced hypercalcaemia; the less frequent ones include thyrotoxicosis, drug-induced conditions (*eg,* thiazide diuretics, lithium, estrogens and antiestrogens, androgens, vitamin A), immobilization, tuberculosis, rabdomyolysis, sarcoidosis, total parenteral nutrition, milk-alkali syndrome, kidney disease (acute and chronic, usually from medications) and familial hypocalciuric hypercalcaemia.

Although careful examination of personal and family history - focusing on clinical manifestations of hypercalcaemia and risk factors for malignancy and causative therapies - physical examination and laboratory investigations can differentiate the causes in most cases, hypercalcaemia often remains a challenging disease for clinicians.

4. PRIMARY HYPERPARATHYROIDISM AND HUMORAL HYPERCALCAEMIA

Identifying the aetiology of hypercalcaemia is very important, since subsequent management differs according to pathology. The main challenge in management is distinguishing the IPHP from conditions that will not respond to parathyroidectomy.

PTH level is the classic discriminator between parathyroid disease-dependent hypercalcaemia and others, whereas PTHrP - identified as tumour-associated factor - is the most useful analytical method in HHM.

The humoral hypercalcemia of malignancy is one of the most frequent paraneoplastic syndromes and it is reported in up to 20 to 30% of patients with cancer (6-12).

In 1889, Stephen Paget stated that “in a cancer of the breast the bones suffer in a special way, which cannot be explained by any theory of embolism alone…the same thing is seen much clearly in those cases of cancer of the thyroid body where secondary deposition occurs in bones with astonishing frequency” and furthermore that “a general degradation of the bones sometimes occurs in carcinoma of the breast, yet without any distinct deposition of cancer in them” (13). Therefore, the current consideration that the cancer affects bone both by direct metastatic localization and through systemic humoral mechanism[6] had been presciently recognized.

However, hypercalcaemia has only been associated with malignancy since 1920, when the serum calcium assay was introduced to clinical practice (6,14) and, in 1987, parathyroid-hormone-related peptide was isolated as a causative factor of HHM from human lung cancer (15) breast cancer (16) and renal cell carcinoma (17) and cloned shortly after its discovery (18).

5. PARATHYROID HORMONE-RELATED PROTEIN

This hormone is produced by a different gene - located on distinct chromosomes compared with PTH (mapped to the short arm of chromosome 12 and 11, respectively) - as a 141-amino acid protein or as a protein comprising either 139 or 173 amino acids, through different mRNA splicing (19).

Subsequently, PTHrP was detected in numerous tumour types like prostate cancer (20-22), epithelioid leiomyosarcoma (23), uterine carcinoma (24), cancer of the exocrine pancreas (10), pancreatic neuroendocrine tumour (25,26), squamous cell carcinoma (27-31), medulloblastoma (32), craniopharingioma (33), rhabdomyosarcoma (34,35), haematological tumors (36-38), tumors of the neck and head (39-42), carcinoma of ovary (43,44), gallbladder carcinoma (45), cholangiocellular carcinoma (46,47), colorectal adenocarcinoma (48-52), carcinoma of the stomach (53), and melanoma (54).

PTHrP mediated hypercalcemia has already been reported in benignancy on rare occasions (55-58). Indeed, the presence of the hormone has been described in cases of gastrointestinal stromal tumours, leiomyoma and schwannoma (59), pheochromocytoma (60-62), mammary hyperplasia (63), uterine leiomyoma (64,65), as well as in other diseases, such as osteoporosis, sepsis, atherosclerosis,

hypertension and chronic inflammatory/autoimmune diseases (66-70).

Although PTHrP is undetectable in the circulating blood of normal subjects, this humoral factor is also produced by several normal tissues, suggesting that the hormone has a role in normal physiology as a local regulator in a paracrine/autocrine manner (6-71).

A role of PTHrP in the regulating cartilage differentiation and bone formation (72,73), in the growth and maturation of skin, mammary glands and teeth (74-76), and in lung development (77), has been demonstrated in recent studies.

Further interaction has been observed in the cardiovascular function (78,79), in the transepithelial calcium transport in mammary epithelia and placenta (80,81), in the relaxation of smooth muscle in uterus, bladder, vessels and ileum (82-85), and in the host immune function (86,87).

Other effects are the increase of beta cell mass and insulin secretion in the pancreas (88-91), and the involvement in the central nervous system function (92-96).

PTHrP has been demonstrated in adult human parathyroid tissue under normal and pathological conditions (5), and the release of this hormone from the human parathyroid cells into the extracellular space has been demonstrated to depend on the extracellular calcium concentration (97).

However, the main effect of PTHrP is the interaction on bone growth and development and it is mediated by PTH type 1 receptor (PTH1R) binding, a G protein (98). The reaction with PTH1R in the bone and kidney results in the increase of the calcium serum level; therefore the biological responses elicited by PTH and PTHrP through this common PTH1R are largely indistinguishable, at least as regards mineral ion homeostasis (99-103), PTHrP stimulates bone resorption and mimics all PTH-like effects on tubules, including calcemic and phosphaturic effects.

The hormone binds to PTH1R with a high affinity, in the same way as PTH. These hormones' amino-terminal (1-34) peptide fragments are considered sufficient to achieve efficient receptor activation and action on mineral ion homeostasis (99-102).

PTHrP actually shows significant sequence homology with PTH within the first 13 amino acid residues, and this fragment conservation explains the similar function of the amino-terminal residues in receptor signalling (101-106).

Indeed, the homology between PTHrP and PTH decreases markedly in the 14-34 sequence, because only three amino acids are identical, and these hormones are completely different beyond residue 34.

Several evidence suggests that midregional and/or carboxy-terminal fragments of PTHrP and PTH also have biological activities (81,107,108), which are not likely to be related to mineral ion homeostasis and are probably mediated by other, not yet defined receptors (109-111).

However, the main PTH1R binding domain of PTHrP is localized in the 15-34 region peptide, and it is the same for PTH (112,113). Therefore, despite the absence of homology, the two different receptor-binding domains of PTHrP and PTH adopt a similar conformation. Indeed, the early N-terminal sequence of each hormone is required for biological activity, allowing the activation of the adenylyl cyclase/protein kinase A (AC/PKA) pathway.

This pathway and the phospholipase C/protein kinase C (PLC/PKC) pathway are at least the two second messenger signalling systems activated by PTHrP and PTH (107,114).

Currently the non-adenylyl-cyclase-mediated pathway is considered more complex than the AC/PKA system, because of the multiple phospholipase isoforms involvement, the sensitivity to variations in cell type and in receptor density (115,117).

The possibility of N-terminal PTHrP fragments activating a novel receptor in keratynocytes, insulinoma cells, lymphocytes and squamous carcinoma cells has been demonstrated; the activation determines the increase of intracellular free calcium, but not cAMP (90,118).

6. PARATHYROID HORMONE-RELATED PROTEIN AND PARATHYROID ADENOMA

Although the production of PTHrP secondary to parathyroid adenomas has been reported (5,119-122), this seem to be the first review in literature investigating the incidence of primary hyperparathyroidism with hypercalcemia and expression of PTHrP in association or not to the hypersecretion of PTH.

Primary hyperparathyroidism indicates the inappropriate or unregulated overproduction of PTH leading to abnormal calcium homeostasis. The effects of hypersecretion of PTH are the increase of renal resorption of calcium, bone resorption, synthesis of 1,24-dihydroxyvitamin D3 (1,24 (OH)2D3) and phosphaturia (123).

Generally, laboratory hallmarks are hypercalcemia, hypophosphataemia, hypercalciuria, elevated serum PTH levels and undetectable plasma levels of PTHrP. Most patients are asymptomatic or mildly symptomatic and the symptoms are correlated with hypercalcemia (124-127).

PHPT is secondary to an adenoma of the parathyroid gland accounting for 80% to 85%, a hyperplasia, for 10%-15%, and a carcinoma, for less than 1% (124,125,128,129).

Table 1. Primary hyperparathyroidism with hypercalcaemia and normal level of PTH: literature review

Author	Number of cases
Bhadada SK, 2008 (168)	2
Gurrado A, 2008 (169)	1
Khoo TK, 2007 (170)	1
Lafferty FW, 2006 (171)	1
Bergenfelz A, 2003 (2)	20
Perez JB, 2001 (119)	1
Bundgaard MJ, 2000 (172)	1
Marcinkowski W, 2000 (173)	22
Mischis-Troussard C, 2000 (174)	20
Baugmart DC, 1998 (175)	1
Glendnning P, 1998 (4)	11
Haddock L, 1998 (176)	5
Okazaki R, 1992 (177)	3
Bergenfelz A, 1991 (178)	6
Hollenberg AN, 1991 (120)	1
Broughan TA, 1986 (179)	36
Coetzee J, 1980 (180)	1
Setton HV, 1979 (181)	1
Hammonds JC, 1976 (182)	23
Total	***157***

The parathyroid adenoma has been reported to be ectopic in 5 to 10% of cases (130), and this evidence is a frequent cause of surgical failure, requiring preoperative imaging to localise the condition in patients with PHPT before initiating surgery. Indeed, about 5% of patients who underwent parathyroidectomy present persistent or recurrent hyperparathyroidism (131).

The main cell types in parathyroid adenoma are chief cells, oxyphil and/or transitional oxyphil cells. Generally, PHPT is secondary to a solitary adenoma composed mainly of chief cells producing PTH. Indeed, the histology referring to an oxyphil adenoma is not commonly reported. This is an infrequent histological form considered exclusively non-functioning until 1970, consisting of cells with abundant eosinophilic cytoplasm that correlates ultrastructurally with numerous mitochondria (132).

In order to identify an oxyphil adenoma, the following histological criteria should be respected: 1) at least 90% of the cells should be oxyphil; 2) histologically normal excision or biopsy of a second gland should exclude the possibility of parathyroid hyperplasia; and 3) immediate postoperative normalization of hypercalcaemia should be reported (133).

At present, several Authors have reported cases of oxyphil parathyroid adenoma producing PTH (133-164).

Since the introduction of the intact PTH assay (immunoradiometric assay, IRMA) in 1984, the PTH level is high or included in the upper third of the normal range in order to diagnose PHPT (165-167).

The literature review regarding the reported cases of surgically proven PHPT with hypercalcaemia and normal levels of PTH has been reported (Table 1).

Several hypotheses have been performed in literature to explain the correlation between the atypical biochemical presentation and the histology of adenoma of parathyroid in these cases. There are quite a few pathological conditions, like coexistent sarcoidosis and/or vitamin D toxicity and/or hypomagnesaemia, which might suppress intact PTH level (183,184).

Another cause is related to the heat-lability/fragility of the hormone that degrades rapidly if the "cold chain" is not guaranteed during sample collection and transportation (185).

Moreover, an intact PTH level difference can be secondary to various methods, including the IRMA and immunochemiluminescent assay (ICMA) The IRMA is a "sandwich" assay formed by the solid-phase antibody, the antigen and the excess labelled antibody. In the event of an elevated concentration of antigen and insufficient solid-phase antibody, the unreacted antigen in solution competes with the antigen already extracted onto the solid-phase antibody for labelled antibody. Therefore, the count in the solid phase declines with the increase of the level of the antigen, inverting the dose-response curve, and determining the "hook effect" (186). However, this phenomenon might be avoided through serial dilution serum intact PTH assays (171), or through the ICMA method (168).

The intact PTH level should always be measured on more than two occasions with similar results in each patient.

In literature, the secretion of biologically active PTH fragment by adenoma has been considered, resulting from a post-translational change in the molecule that is not measurable by the current assay (171).

Hollemberg *et al*. (120) proposed different theories to explain the mechanism of the inappropriately low PTH level in the PHPT case observed: 1) the presence of a circulating PTH inhibitor; 2) the pulsatile secretion of the hormone; 3) an abnormal PTH molecule with increased biologic activity; 4) a rise of peripheral tissue sensitivity to normal PTH, 5) the presence of another mediator of hypercalcaemia (eg, PTHrP).

None of these hypotheses has been verified until 2008, when the association of immunohistochemical

Table 2. PHPT due to parathyroid adenoma producing PTHrP: literature review

Author	n. of cases	hypercalcaemia	Serum PTH	Histology of adenoma	PTHrP immunoreactivity	PTHrP gene mRNA
Gurrado A, 2008 (169)	1	*yes*	*n*	*o*	+	*n.r.*
Kitazawa R, 2002 (36)	11	*yes*	*n.r.*	*o*	+	+
Matsushita H, 1997 (187)	9	*yes*	*e*	*n.r.*	+	+
Matsushita H, 1992 (122)	13	*yes*	*e*	*1 o; 11 co; 1c*	+	*n.r.*
Docherty, 1991 (188)	11	*yes*	*e*	*n.r.*	+ *(4/11)*	+ *(7/11)*
Danks JA, 1990 (189)	14	*yes (12/14)* *no (2/14)*	*e (10/14)* *n.r. (4/14)*	*n.r.*	+	*n.r.*
Ikeda, 1989 (5)	40	*n.r.*	*n.r.*	*n.r.*	*n.r.*	+
Total	99					

n: normal; *e :*elevated; *n.r.*: not reported; *n.d.*: not determined; *c*: chief cell type; *o*: oxyphil type; *co*: mixed type.

positivity for PTHrP-antigens, the immediate postoperative normalization of hypercalcaemia, and the histological features of oxyphil parathyroid adenoma were observed in a patient with hypercalcemia and normal serum PTH level (169).

A literature review regarding the parathyroid adenomas positive for PTHrP immunoreactivity or overexpression of the messenger ribonucleic acid (mRNA) of the hormone gene was performed (Table 2).

PTHrP expression in normal or abnormal parathyroid tissue was analysed in some series and, so interestingly the positivity was most frequently related to adenoma with a dominance of oxyphil cells, and very uncommonly to chief cell type or mixed (5,36,121,122).

The age-related increase in oxyphil cells explains the frequency of immunohistochemical detection of PTHrP in normal parathyroid in adult population. Several studies have, indeed, defined the correlation of this hormone with the age-related metaplastic change of parathyroid cells into the oxyphil phenotype, through a paracrine/autocrine regulation mechanism (36,122).

Besides the same target, the PTH and PTHrP have been demonstrated to be secreted simultaneously by parathyroid adenoma cells and inversely related to the extracellular calcium ion concentration (97). *Matsushita et al.* [187] demonstrated furthermore that PTHrP could be co-secreted by the parathyroid gland together with PTH via a regulated pathway and that a constitutive pathway could barely operate in the secretory mechanism of PTHrP in parathyroid adenoma cells.

At present, the role of PTHrP secreted by reported cases of oxyphil parathyroid adenoma associated with hypercalcaemia has not been explicated (Table 2). In most series, the PTH level has not been reported (5,36,189), and in others, the hypercalcaemia depended on the simultaneous hypersecretion of PTH (122,187-189).

Although there are discordant opinions (137,190-192,194,195), several Authors observed a statistically significant rise of Tc-99m-sestamibi scan sensitivity of oxyphil adenoma, due to affinity of the mitochondrial-rich cell for the sestamibi uptake and retention (134,140,143,193-195). This should be considered an important factor in order to perform the diagnosis of adenoma in the unusual biochemical cases of PHPT.

To the best of our knowledge, one is the report regarding the association of immunohistochemical positivity for PTHrP-antigens with normal serum PTH level, the immediate postoperative normalization of hypercalcaemia, and the histological features of parathyroid adenoma (169).

7. SUMMARY AND PERSPECTIVE

Despite considerable advances in the understanding of the synthesis, secretion, molecular structure and target activation of PTH and PTHrP, hypercalcaemia can sometimes, but rarely, represent a diagnostic dilemma and a therapeutic challenge.

PTHrP could play a critical role in determining the pathogenesis of atypical biochemical presentation of hypercalcaemia due to parathyroid adenoma and the PTHrP measurement should be assessed not only in the presence of malignancy. Moreover, the diagnostic suspicion of PHPT should not be eliminated when serum PTH levels are in normal range.

Further research with larger populations is necessary to define a novel diagnostic flow-chart of hypercalcaemia considering the whole of the clinical and biochemical presentations of PHPT.

8. REFERENCES

1. G.J. Strewler: The physiology of parathyroid hormone-related protein. *N England J Med* 342, 177-185 (2000)

2. A. Bergenfelz, P. Lindblom, B. Lindegard, S. Valdemarsson and J. Westerdahl: Preoperative normal level of parathyroid hormone signifies an early and mild form of primary hyperparathyroidism. *World J Surg* 27, 481-5 (2003)

3. G.B. Talpos, H.G. Bone 3rd, M. Kleerekoper, E.R. Phillips, M. Alam, M. Honasoge, G.W. Divine and D.S. Rao: Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey. *Surgery* 128, 1013-20 (2000)

4. P. Glendenning, D.H. Gutteridge, R.W. Retallack, B.G. Stuckey, D.G. Kermode and G.N. Kent: High prevalence of normal total calcium and intact PTH in 60 patients with proven primary hyperparathyroidism: a challenge to current diagnostic criteria. *Aust N Z J Med* 28, 173-8 (1998)

5. K. Ikeda, A. Arnold, M. Mangin, B. Kinder, N.A. Vydelingum, M.F. Brennan and A.E. Broadus: Expression of transcripts encoding a parathyroid hormone-related peptide in abnormal human parathyroid tissues. *J Clin Endocrinol Metab* 69, 1240-8 (1989)

6. G.A. Clines and T.A. Guise: Hypercalcaemia of malignancy and basic research on mechanisms responsible for osteolytic and osteoblastic metastasis to bone. *Endocr Relat Cancer* 12, 549-83 (2005)

7. M.L. Farias: Hypercalcemia of malignancy: features, diagnosis and treatment. *Arq Bras Endocrinol Metabol* 49, 816-24 (2005)

8. V. Grill and T.J. Martin: Hypercalcemia of malignancy. *Rev Endocr Metab Disord* 1, 253–263 (2000)

9. R.A. DeLellis and L. Xia: Paraneoplastic endocrine syndromes: a review. *Endocr Pathol* 14, 303-17 (2003)

10. P. Bandyopadhyay, S. Baksi, D. Bandyopadhyay and C.U. Patel: Parathyroid hormone-related protein in pancreatic exocrine cancer associated with hypercalcaemia. *Int J Clin Pract* 57, 140-2 (2003)

11. M.C. Bayne and T.M. Illidge: Hypercalcaemia, parathyroid hormone-related protein and malignancy. *Clin Oncol (R Coll Radiol)* 13, 372-7 (2001)

12. P. Esbrit: Hypercalcemia of malignancy: new insights into an old syndrome. *Clin Lab* 47, 67-71 (2001)

13. S. Paget: The distribution of secondary growths in cancer of the breast. 1889. *Cancer Metastasis Rev* 8, 98-101 (1989)

14. A.J. Swyer, J.S. Berger, H.M. Gordon and D. Laszlo: Hypercalcemia in osteolytic metastatic cancer of the breast. *Am J Med* 8, 724-32 (1950)

15. J.M. Moseley, M. Kubota, H. Diefenbach-Jagger, R.E. Wettenhall, B.E. Kemp, L.J. Suva, C.P. Rodda, P.R. Ebeling, P.J. Hudson, J.D. Zajac and T.J. Martin: Parathyroid hormone related protein purified from a human lung cancer cell line. *Proc Natl Acad Sci USA* 84, 5048–5052 (1987)

16. W.J. Burtis, T.G. Brady, J.J. Orloff, J.B. Ersbak, R.P. Warrell Jr, B.R. Olson, T.L. Wu, M.E. Mitnick, A.E. Broadus and A.F. Stewart: Immunochemical characterization of circulating parathyroid hormone-related protein in patients with humoral hypercalcemia of cancer. *New England Journal of Medicine* 322, 1106–1112 (1990)

17. G.J. Strewler, P.H. Stern, J.W. Jacobs, J. Eveloff, R.F. Klein, S.C. Leung, M. Rosenblatt and R.A. Nissenson: Parathyroid hormonelike protein from human renal carcinoma cells. Structural and functional homology with parathyroid hormone. *Journal of Clinical Investigation* 80, 803–1807 (1987)

18. L.J. Suva, G.A. Winslow, R.E. Wettenhall, R.G. Hammonds, J.M. Moseley, H. Diefenbach-Jagger, C.P. Rodda, B.E. Kemp, H. Rodriguez, E.Y. Chen, P.J. Hudson, T.J. Martin and W.I. Wood: A parathyroid hormone-related protein implicated in malignant hypercalcemia: cloning and expression. *Science* 237, 893–896 (1987)

19. W.J. Burtis: Parathyroid hormone-related protein: structure, function and measurement. *Clin Chem* 38, 2171-83 (1992)

20. J. Liao, X. Li, A.J. Koh, J.E. Berry, N. Thudi, T.J. Rosol, K.J. Pienta and L.K. McCauley: Tumor expressed PTHrP facilitates prostate cancer-induced osteoblastic lesions. *Int J Cancer* 123, 2267-78 (2008)

21. C. Soubier and T. Massfelder: Parathyroid hormone-related protein in human renal cell carcinoma. *Cancer Lett* 240, 170-82 (2006)

22. F. Asadi and S. Kukreja: Parathyroid hormone-related protein in prostate cancer. *Crit Rev Eukaryot Gene Expr* 15, 15-28 (2005)

23. S.J. Tang, S. Geevarghese, S. Saab, D. Martinez, A. Van Herle, W.D. Wallace, G.R. Cortina, S. Dry and R.W. Busuttil: A parathyroid hormone-related protein – secreting metastatic epithelioid leiomyosarcoma. A case report and review of the literature. *Arch Pathol Lab Med* 127, 181-5 (2003)

24. Y. Kinugasa, K. Morishige, S. Kamiura, Y. Tsukamoto and F. Saji: Parathyroid hormone-related protein-secreting uterine endometrioid adenocarcinoma. *Jpn J Clin Oncol* 36, 113-5 (2006)

25. K. Mussig, S. Petersenn, M. Wehrmann, M. Horger, P. Vierling, H.U. Haring and B. Gallwitz: Somatostatin receptor expression in a parathyroid hormone-related peptide-secreting pancreatic neuroendocrine tumour causing severe hypercalcaemia. *Eur J Gastroenterol Hepatol* 19, 719-23 (2007)

26. G.G. Van den Eynden, A. Neyret, G. Fumey, M. Rizk-Rabin, P.B. Vermeulen, Z. Bouizar, J.J. Body and L.Y. Dirix: PTHrP, calcitonin and calcitriol in a case of severe, protracted and refractory hypercalcemia due to a pancreatic neuroendocrine tumor. *Bone* 40, 1166-71 (2007)

27. K. Tamura, T. Yoshinaga, M. Tanino, T. Kimura, N. Yamada, M. Nishimura, S. Fukuda, H. Nishihara, M. Shindoh and S. Tanaka: Hypopharyngeal squamous cell carcinoma producing both granulocyte colony-stimulating factor and parathyroid hormone-related protein. *Pathol Int* 58, 652-6 (2008)

28. S. Washino, F. Terauchi, A. Matsuzaki and Y. Kobayashi: Two cases of squamous cell carcinoma of upper urinary tract with hypercalcemia. *Nippon Hinyokika Gakkai Zasshi* 99, 703-8 (2008)

29. N. Asanuma, K. Hagiwara, I. Matsumoto, M. Matsuda, F. Nakamura, H. Kouhara, M. Miyamoto, Y. Miyashita, S. Noguchi and Y. Morimoto: PTHrP – producing tumor: squamous cell carcinoma of the liver accompanied by humoral hypercalcemia of malignancy, increased IL-6 and leucocytosis. *Intern Med* 41, 371-6 (2002)

30. T.J. Martin and V. Grill: Hypercalcemia in cancer. *J Steroid Biochem Mol Biol* 43, 123-9 (1992)

31. T.J. Martin and P.R. Ebeling: A novel parathyroid hormone-related protein: role in pathology and physiology. *Prog Clin Biol Res* 332, 1-37 (1990)

32. M. Gessi, G. Monego, G. Calviello, P. Lanza, F. Giangaspero, A. Silvestrini, L. Lauriola and F.O. Ranelletti: Human parathyroid hormone-related protein and human parathyroid hormone receptor type 1 are expressed in human medulloblastomas and regulate cell proliferation and apoptosis in medulloblastoma-derived cell lines. *Acta Neuropathol* 114, 135-45 (2007)

33. J.L. Brown, D.W. Burton, L.J. Deftos, A.A. Smith, D.W. Pincus and M.J. Haller: Congenital craniopharyngioma and hypercalcemia induced by parathyroid hormone-related protein. *Endocr Pract* 13, 67-71 (2007)

34. J.C. Florez, D.W. Burton, P.M. Arnell, L.J. Deftos and A. Klibanski: Hypercalcemia and local production of parathyroid hormone-related protein by a perisellar rhabdomyosarcoma after remote pituitary irradiation. *Endocr Pract* 11, 184-9 (2005)

35. K. Wong, S. Tsuda, R. Mukai, K. Sumida and R. Arakaki: Parathyroid hormone expression in a patient with metastatic nasopharyngeal rhabdomyosarcoma and hypercalcemia. *Endocrine* 27, 83-6 (2005)

36. R. Kitazawa, S. Kitazawa, K. Kajimoto, T. Sugimoto, T. Matsui, K. Chihara and S. Maeda: Expression of parathyroid hormone-related protein (PTHrP) in multiple myeloma. *Pathol Int* 52, 63-8 (2002)

37. B. Schottker, W. Heinz, F. Weissinger, K. Sozener, M. Eck and J. Seufert: Parathyroid-hormone-related-protein-associated hypercalcemia in a patient with CLL-type low-grade leukemic B-cell lymphoma. *Haematologica* 91 (12 Suppl), ECR45 (2006)

38. H. Niizuma, K. Fujii, A. Sato, I. Fujiwara, J. Takeyama and M. Imaizumi: PTHrP-independent hypercalcemia with increased proinflammatory cytokines and bone resorption in two children with CD19-negative precursor B acute lymphoblastic leukemia. *Pediatr Blood Cancer* 49, 990-3 (2007)

39. A. Dackiw, J. Pan, G. Xu and S.C. Yeung: Modulation of parathyroid hormone-related protein levels (PTHrP) in anaplastic thyroid cancer. *Surgery* 138, 456-63 (2005)

40. M.H. Lam, R.J. Thomas, T.J. Martin, M.T. Gillespie and D.A. Jans: Nuclear and nucleolar localization of parathyroid hormone-related protein. *Immunol Cell Biol* 78, 395-402 (2000)

41. J.T. Brawner and R.P. Zitsch 3rd: Parathyroid hormone-related peptide as a cause of hypercalcemia in squamous cell carcinoma of the head and neck: a case presentation and subject review. *Head Neck* 26, 382-4 (2004)

42. F. Yoshiike, T. Koizumi, A. Yoneyama, M. Komatu, S. Yamaguchi, M. Hanaoka, K. Kubo and S. Eda: Thymic squamous cell carcinoma producing parathyroid hormone-related protein and CYFRA 21-1. *Intern Med* 43, 493-5 (2004)

43. N. Suwaki, H. Masuyama, Y. Mizutani, J. Kodama and Y. Hiramatsu: Parathyroid hormone-related protein as a potential tumor marker: a case report of ovarian clear cell carcinoma. *J Obstet Gynaecol Res* 32, 94-8 (2006)

44. T. Fujino, T. Watanabe, K. Yamaguchi, K. Nagasaki, E. Onoshi, I. Iwamoto, H. Dozono and Y. Nagat: The development of hypercalcemia in a patient with an ovarian tumor producing parathyroid hormone-related protein. *Cancer* 70, 2845-50 (1992)

45. Y. Imoto, N. Muguruma, T. Kimura, M. Kaji, H. Miyamoto, S. Okamura, S. Ito, M. Nakasono, M. Hirokawa and T. Sano: A case of parathyroid hormone-related peptide producing gallbladder carcinoma presenting humoral hypercalcemia of malignancy. *Nippon Shokakibyo Gakkai Zasshi* 104, 401-6 (2007)

46. Y. Yen, P.G. Chu and W. Feng: Paraneoplastic syndromes in cancer: Case 3. Parathyroid hormone-related hypercalcemia in cholangiocarcinoma. *J Clin Oncol* 22, 2244-5 (2004)

47. T. Sohda, H. Shiga, H. Nakane, H. Watanabe, M. Takeshita and S. Sakisaka: Cholangiocellular carcinoma that produced both granulocyte-colony-stimulating factor and parathyroid hormone-related protein. *Int J Clin Oncol* 11, 246-9 (2006)

48. M. Nishihara, T. Kanematsu, T. Taguchi, M.S. Razzaque: PTHrP and tumorogenesis: is there a role in prognosis? *Ann N Y Acad Sci* 1117, 385-92 (2007)

49. J. Sakata, T. Wakai, Y. Shirai, E. Sakata, G. Hasegawa and K. Hatakeyama: Humoral hypercalcemia complicating adenocarcinoma of the sigmoid colon: report of a case. *Surg Today* 35, 692-5 (2005)

50. J.Y. Luh, E.S. Han, J.R. Simmons and R.P. Whitehead: Poorly differentiated colon carcinomawith neuroendocrine features presenting with hypercalcemia and cutaneous metastases: case report and review of the literature. *Am J Clin Oncol* 25, 160-3 (2002)

51. J.T. Thompson, E.H. Paschold and E.A. Levine: Paraneoplastic hypercalcemia in a patient with adenosquamous cancer of the colon. *Am Surg* 67, 585-8 (2001)

52. A.H. Lortholary, S.D. Cadeau, G.M. Bertrand, V.I. Guerin-Meyer, E.C. Gamelin and M.J. Audran: Humoral hypercalcemia in patients with colorectal carcinoma: report of two cases and review of the literature. *Cancer* 86, 2217-21 (1999)

53. S. Yamashita, N. Takahashi, H. Hashimoto, T. Tachibana, T. Nakahara, A. Ohyama and K. Yanaga: Establishment and characterization of a cell line (IGSK-3) secreting human chorionic gonadotropin, adrenocorticotropic hormone and parathyroid hormone-related protein derived from primary poorly differentiated adenocarcinoma of the stomach. *Hum Cell* 21, 88-94 (2008)

54. U. Trefzer, K. Pelzer, M.A. Hofmann and W. Sterry: Parathyroid hormone-related protein-induced hypercalcaemia in metastatic melanoma. *J Eur Acad Dermatol Venereol* 20, 346-7 (2006)

55. T.P. Knecht, C.A. Behling, D.W. Burton, C.K. Glass and L.J. Deftos: The humoral hypercalcemia of benignancy: a newly appreciated syndrome. *Am J Clin Pathol* 105, 487-492 (1996)

56. R. Herring and K. Laji: Humoral hypercalcemia of benignancy. A case report. *QJM* 101, 329-30 (2008)

57. T.P. Knecht, C.A. Behling, D.W. Burton, C.K. Glass and L.J. Deftos: Humoral hypercalcemia of "benignancy". *Lancet* 346, 711-2 (1995)

58. D.E. Bruns and M.E. Bruns: Parathyroid hormone-related protein in benign lesions. *Am J Clin Pathol* 105, 377-9 (1996)

59. A. Yoshizaki, T. Nakayama, S. Naito and I. Sekine: Expressions of parathyroid hormone-related protein (PTHrP) and PTH/PTHrP-receptor (PTH/PTHrP-R) in gastrointestinal stromal tumours (GISTs), leiomyomas and schwannomas. *Scand J Gastroenterol* 39, 133-7 (2004)

60. T. Mune, H. Katakami, Y. Kato, K. Yasuda, S. Matsukura and K. Miura: Production and secretion of parathyroid hormone-related protein in pheochromocytoma: participation of an alpha-adrenergic mechanism. *J Clin Endocrinol Metab* 76, 757-62 (1993)

61. J.A. Bridgewater, W.A. Ratcliffe, N.J. Bundred and C.W. Owens: Malignant phaeochromocytoma and hypercalcaemia. *Postgrad Med* J 69, 77-9 (1993)

62. S. Kimura, Y. Nishimura, K. Yamaguchi, K. Nagasaki, K. Shimada and H. Uchida: A case of pheochromocytoma producing parathyroid hormone-related protein and presenting with hypercalcemia. *J Clin Endocrinol Metab* 70, 1559-63 (1990)

63. S. Khosla, J.A. van Heerden, H. Gharib, I.T. Jackson, J. Danks, J.A. Hayman, T.J. Martin: Parathyroid hormone-related protein and hypercalcemia secondary to massive mammary hyperplasia. *N Engl J Med* 322, 1157 (1990)

64. K. Ravakhah, A. Gover and B.N. Mukunda: Humoral hypercalcemia associated with uterine fibroid. *Ann Intern Med* 130, 702 (1999)

65. S. Dagdelen, I. Kalan and A. Gurlek: Humoral hypercalcemia of benignancy secondary to parathyroid hormone–related protein secreting uterine leiomyoma. *Am J Med Sci* 335, 407-8 (2008)

66. T. Massfelder and J.J. Helwig: The parathyroid hormone-related protein system: more data but more unsolved questions. *Curr Opin Nephrol Hypertens* 12, 35-42 (2003)

67. J.L. Funk: A role for parathyroid hormone-related protein in the pathogenesis of inflammatory/autoimmune diseases. *Int Immunopharmacol* 1, 1101-21 (2001)

68. J.L .Funk, C.R. Trout, H. Wei, G. Stafford and S. Reichlin: Parathyroid hormone-related protein (PTHrP) induction in reactive astrocytes following brain injury: a possible mediator of CNS inflammation. *Brain Res* 915, 195-209 (2001)

69. A. Ortega, M.T. Perez de Prada, P.J. Mateos-Caceres, P. Ramos Mozo, J.J. Gonzalez-Armengol, J.M. Gonzalez Del Castillo, J. Martín Sanchez, P. Villarroel, J.L. Santiago, R.J. Bosch, C. Macaya, P. Esbrit and A.J. Lopez-Farre: Effect of parathyroid hormone-related protein on human platelet activation. *Clin Sci (Lond)* 113, 319-27 (2007)

70. E. Gomez-Barrena, O. Sanchez-Pernaute, R. Largo, E. Calvo, P. Esbrit, G. Herrero-Beaumont: Sequential changes of parathyroid hormone related protein (PTHrP) in articular cartilage during progression of inflammatory and degenerative arthritis. *Ann Rheum Dis* 63, 917-22 (2004)

71. T.L. Clemens, S. Cormier, A. Eichinger, K. Endlich, N. Fiaschi-Taesch, E. Fischer, P.A. Friedman, A.C. Karaplis, T. Massfelder, J. Rossert, K.D. Schluter, C. Silve, A.F. Stewart, K. Takane and J.J. Helwig: Parathyroid hormone-related protein and its receptors: nuclear functions and roles in the renal and cardiovascular systems, the placental trophoblasts and the pancreatic islets. *Br J Pharmacol* 134, 1113-36 (2001)

72. E. Minina, H.M. Wenzel, C. Kreschel, S. Karp, W. Gaffield, A.P. McMahon and A. Vortkamp: BMP and Ihh/PTHrP signaling interact to coordinate chondrocyte proliferation and differentiation. *Development* 128, 4523–4534 (2001)

73. N. Amizuka, J.E. Henderson, J.H. White, A.C. Karaplis, D. Goltzam, T. Sasaki and H. Ozawa: Recent studies on the biological action of parathyroid hormone (PTH)-related peptide (PTHrP) and PTH/PTHrP receptor in cartilage and bone. *Histol Histopathol* 15, 957-70 (2000)

74. J.J. Wysolmerski, A.E. Broadus, J. Zhou, E. Fuchs, L.M. Milstone and W.M. Philbrick: Overexpression of parathyroid hormone-related protein in the skin of transgenic mice interferes with hair follicle development. *Proc Natl Acad Sci USA* 91, 1133–1137 (1994)

75. J.J. Wysolmerski, W.M. Philbrick, M.E. Dunbar, B. Lanske, H. Kronenberg and A.E. Broadus: Rescue of the parathyroid hormone-related protein knockout mouse demonstrates that parathyroid hormone-related protein is essential for mammary gland development. *Development* 125, 1285–1294 (1998)

76. W.M. Philbrick, B.E. Dreyer, I.A. Nakchbandi and A.C. Karaplis: Parathyroid hormone-related protein is required for tooth eruption. *Proc Natl Acad Sci USA* 95, 11846–11851 (1998)

77. R.H. Hastings, J.T. Berg, D. Summers-Torres, D.W. Burton and L.J. Deftos: Parathyroid hormone-related protein reduces alveolar epithelial cell proliferation during lung injury in rats. *Am J Physiol Lung Cell Mol Physiol* 279, L194 ± L200 (2000)

78. K.D. Schluter and H.M. Piper: Cardiovascular actions of parathyroid hormone and parathyroid hormonerelated peptide. *Cardiovascular Research* 37, 34–41 (1998)

79. A. Halapas, R. Tenta, C. Pantos, D.V. Cokkinos and M. Koutsilieris: Parathyroid hormone-related peptide and cardiovascular system. *In vivo* 17, 425-32 (2003)

80. J.J. Wysolmerski, J.M. Carucci, A.E. Broadus and W.M. Philbrick: PTH and PTHrP antagonize mammary gland growth and development in transgenic mice. *Journal of Bone and Mineral Research* 9, S121 (1994)

81. C.S. Kovacs, B. Lanske, J.L. Hunzelman, J. Guo, A.C. Karaplis and H.M. Kronenberg: Parathyroid hormone-related peptide (PTHrP) regulates fetal-placental calcium transport through a receptor distinct from the PTH/ PTHrP receptor. *Proc Natl Acad Sci USA* 93, 15233–15238 (1996)

82. M.A. Thiede, A.G. Daifotis, E.C. Weir, M.L. Brines, W.J. Burtis, K. Ikeda, B.E. Dreyer, R.E. Garfield and A.E. Broadus: Intrauterine occupancy controls expression of the parathyroid hormone-related peptide gene in preterm rat myometrium. *Proc Natl Acad Sci USA* 87, 6969–6973 (1990)

83. M. Yamamoto, S.C. Harm, W.A. Grasser and M.A. Thiede: Parathyroid hormone-related protein in the rat urinary bladder: a smooth muscle relaxant produced locally in response to mechanical stretch. *Proc Natl Acad Sci USA* 89, 5326–5330 (1992)

84. A. Botella, M. Rekik, M. Delvaux, M.J. Davicco, J.P. Barlet, J. Frexinos and L. Bueno: Parathyroid hormone (PTH) and PTH-related peptide induce relaxation of smooth muscle cells from guinea pig ileum: interaction with vasoactive intestinal peptide receptors. *Endocrinology* 135, 2160–2167 (1994)

85. C.J. Pirola, H.M. Wang, M.I. Strgacich, A. Kamyar, B. Cercek, J.S. Forrester, T.L. Clemens and J.A. Fagin: Mechanical stimuli induce vascular parathyroid hormone-related protein gene expression *in vivo* and *in vitro*. *Endocrinology* 134, 2230–2236 (1994)

86. J.L. Funk, J.K. Shigenaga, A.H. Moser, E.J. Krul, G.J. Strewler, K.R. Feingold and C. Grunfeld: Cytokine regulation of parathyroid hormone-related protein messenger ribonucleic acid levels in mouse spleen: paradoxical effects of interferon-gamma and interleukin-4. *Endocrinology* 135, 351–358 (1994)

87. J.L. Funk, J. Lausier, A.H. Moser, J.K. Shigenaga, S. Huling, R.A. Nissenson, G.J. Strewler, C. Grunfeld and K.R. Feingold: Endotoxin induces parathyroid hormone-related protein gene expression in splenic stromal and smooth muscle cells, not in splenic lymphocytes. *Endocrinology* 136, 3412–3421 (1995)

88. R.C. Vasavada, A. Garcia-Ocana, W.S. Zawalich, R.L. Soren-Son, P.S. Dann, L. Ogren, F. Talamantes and A.F. Stewart: Targeted expression of placental lactogen in the beta cells of transgenic mice results in beta cell proliferation, islet mass augmentation, and hypoglycemia. *J Biol Chem* 275, 15399-15406 (2000)

89. S.E. Porter, R.L. Sorenson, P. Dann, A. Garcia-Ocana, A.F. Stewart and R.C. Vasavada: Progressive pancreatic islet hyperplasia in the islet-targeted, parathyroid hormone-related protein-overexpressing mouse. *Endocrinology* 139, 3743-3751 (1998)

90. G. Gaich, J.J. Orloff, E.J. Atillasoy, W.J. Burtis, M.B. Ganz and A.F. Stewart: Amino-terminal parathyroid hormone-related protein: specific binding and cytosolic calcium responses in rat insulinoma cells. *Endocrinology* 132, 1402-1409 (1993)

91. M.L. Villanueva-Penacarrillo, J. Cancelas, F. de Miguel, A. Redondo, A. Valin, I. Valverde and P. Esbrit: Parathyroid hormone-related peptide stimulates DNA synthesis and insulin secretion in pancreatic islets. *J Endocrinol* 163, 403-8 (1999)

92. N. Chattopadhyay, C. Evliyaoglu, O. Heese, R. Carroll, J. Sanders, P. Black and E.M. Brown: Regulation of secretion of PTHrP by Ca (2+)-sensing receptor in human astrocytes, astrocytomas, and meningiomas. *Am J Physiol Cell Physiol* 279, C691-C699 (2000)

93. M.L. Brines and A.E. Broadus: Parathyroid hormone-related protein markedly potentiates depolarization-induced catecholamine release in PC12 cells via L-type voltage-sensitive $Ca2^{+}$ channels. *Endocrinology* 140, 646-651 (1999)

94. S. Yamamoto, I. Morimoto, K. Zeki, Y. Ueta, H. Yamashita, H. Kannan and S. Eto: Centrally administered parathyroid hormone (PTH)-related protein (1-34) but not PTH (1-34) stimulates arginine-vasopressin secretion and its messenger ribonucleic acid expression in supraoptic nucleus of the conscious rats. *Endocrinology* 139, 383-388 (1998)

95. T. Ono, K. Inokuchi, A. Ogura, Y. Ikawa, Y. Kudo and S. Kawashima: Activity-dependent expression of parathyroid hormone-related protein (PTHrP) in rat cerebellar granule neurons. Requirement of PTHrP for the activity-dependent survival of granule neurons. *J Biol Chem* 272, 14404 -14411 (1997)

96. G. Struckhoff and A. Turzynski: Demonstration of parathyroid hormone-related protein in meninges and its receptor in astrocytes: evidence for a paracrine meningo-astrocytic loop. *Brain Res* 676, 1-9 (1995)

97. H. Matsushita, M. Hara, K. Honda, M. Kuroda, M. Usui, H. Nakazawa, S. Hara and Y. Shishiba: Inibition of parathyroid hormone-related protein release by extracellular calcium in dispersed cells from human parathyroid hyperplasia secondary to chronic renal failure and adenoma. *Am J Pathol* 146, 1-8 (1995)

98. HM. Kronenberg: PTHrP and skeletal development. *Ann NY Acad Sci* 1068, 1-13 (2006)

99. M. Everhart-Caye, S. E. Inzucchi, J. Guinness-Henry, M. A. Mitnick, and A. F. Stewart: Parathyroid hormone (PTH)-related protein (1–36) is equipotent to PTH- (1–34) in humans. *J Clin Endocrinol Metab* 81, 199–208 (1996)

100. L. J. Fraher, A. B. Hodsman, K. Jonas, D. Saunders, C. I. Rose, J. E. Henderson, G. N. Hendy and D. Goltzman: A comparison of the *in vivo* biochemical responses to exogenous parathyroid hormone- (1–34) (PTH- (1–34)) and PTH-related peptide- (1–34) in man. *J Clin Endocrinol Metab* 75, 417–423, (1992)

101. N. Horiuchi, M. P. Caulfield, J. E. Fisher, M. E. Goldman, R. L. McKee, J. E. Reagan, J. J. Levy, R. F. Nutt, S. B. Rodan, T. L. Schofield, T. L. Clemens and M. Rosenblatt: Similarity of synthetic peptide from human tumour to parathyroid hormone *in vivo* and *in vitro*. *Science* 238, 1566–1568 (1987)

102. B. E. Kemp, J. M. Mosely, C. P. Rodda, P. R. Ebeling, R. E. H. Wettenhall, D. Stapleton, H. Diefenbach-Jagger, F. Ure, V. P. Michelangali, H. A. Simmons, L. G. Raisz and T. J. Martin: Parathyroid hormone-related protein of malignancy: active synthetic fragments. *Science* 238, 1568–1570 (1987)

103. M. Mannstadt, H. Juppner and TJ. Gardella: Receptors for PTH and PTHrP: their biological importance and functional properties. *Am J Physiol* 277, F665-75 (1999)

104. J. Guo, A. Iida-Klein, X. Huang, A. B. Abou-Samra, G. V. Segre and F. R. Bringhurst: Parathyroid hormone (PTH)/ PTH-related peptide receptor density modulates activation of phospholipase C and phosphate transport by PTH in LLC-PK1 cells. *Endocrinology* 136, 3884–3891 (1995)

105. N. Horiuchi, M. F. Holick, J. T. Potts, Jr. and M. Rosenblatt: A parathyroid hormone inhibitor *in vivo*: design and biologic evaluation of a hormone analog. *Science* 220, 1053– 1055 (1983)

106. G. W. Tregear, J. Van Rietschoten, E. Greene, H. T. Keutmann, H. D. Niall, B. Reit, J. A. Parsons and J. T. Potts Jr.: Bovine parathyroid hormone: minimum chain length of synthetic peptide required for biological activity. *Endocrinology* 93, 1349–1353 (1973)

107. JT Potts Jr. and H Juppner: Parathyroid hormone and parathyroid hormone-related peptide in calcium homeostasis, bone metabolism, and bone development: the proteins, their genes, and receptors. In: Metabolic Bone Disease, edited by L. V. Avioli and S. M. Krane. New York: *Academic*, 51–94 (1997)

108. T. L. Wu, R. C. Vasavada, K. Yang, T. Massfelder, M. Ganz, S. K. Abbas, A. D. Care and A. F. Stewart: Structural and physiological characterization of the mid-region secretory species of parathyroid hormone-related protein. *J Biol Chem* 271, 24371–24381 (1996)

109. N. Inomata, M. Akiyama, N. Kubota and H. Juppner: Characterization of a novel PTH-receptor with specificity for the carboxyl-terminal region of PTH (1–84) *Endocrinology* 136, 4732–4740 (1995)

110. M. Pines, A. E. Adams, S. Stueckle, R. Bessalle, V. Rashti-Behar, M. Chorev, M. Rosenblatt and L. J. Suva: Generation and characterization of human kidney cell lines stably expressing recombinant human PTH/PTHrP receptor: lack of interaction with a COOH-terminal human PTH peptide. *Endocrinology* 135, 1713–1716 (1994)

111. H. Takasu, H. Baba, N. Inomata, Y. Uchiyama, N. Kubota, K. Kumaki, A. Matsumoto, K. Nakajima, T. Kimura, S. Sakakibara, T. Fujita, K. Chihara and I. Nagai: The 69–84 amino acid region of the parathyroid hormone molecule is essential for the interaction of the hormone with the binding sites with carboxyl-terminal specificity. *Endocrinology* 137, 5537–5543 (1996)

112. A.B. Abou-Samra, S. Uneno, H. Juppner, H. Keutmann, J. T. Potts Jr., G. V. Segre and S. R. Nussbaum. Nonhomologous sequences of parathyroid hormone and the parathyroid hormone related peptide bind to a common receptor on ROS 17/2.8 cells. *Endocrinology* 125, 2215–2217 (1989)

113. M. P. Caulfield and M. Rosenblatt: Parathyroid hormonereceptor interactions. *Trends Endocrinol Metab* 2, 164–168 (1990)

114. G. V. Segre: Receptors for parathyroid hormone and parathyroid hormone-related protein. In: Principles in Bone Biology, edited by J. P. Bilezikian, L. G. Raisz, and G. A. Rodan. New York: *Academic*, 377–403 (1996)

115. P. A. Friedman, F. A. Gesek, P. Morley, J. F. Whitfield and G. E. Willick: Cell-specific signaling and structure-activity relations of parathyroid hormone analogs in mouse kidney cells. *Endocrinology* 140, 301–309 (1999)

116. H. Takasu and F. R. Bringhurst: Type-1 parathyroid hormone (PTH)/PTH-related peptide (PTHrP) receptors activate phospholipase C in response to carboxyl-truncated analogs of PTH- (1–34) *Endocrinology* 139, 4293–4299 (1998)

117. H. Takasu, J. Guo and F. Bringhurst: Dual signaling and ligand selectivity of the human PTH/PTHrP receptor. *J Bone Miner Res* 14, 11–20 (1999)

118. J.J. Orloff, Y. Kats, P. Urena, E. Schipani, R.C. Vasavada, W.M. Philbrick, A. Behal, A.B. Abou-Samra, G.V. Segre and H. Juppner: Further evidence for a novel receptor for amino-terminal parathyroid hormone-related protein on keratinocytes and squamous carcinoma cell lines. *Endocrinology* 136, 3016-3023 (1995)

119. JB Perez and AG Pazianos. Unusual presentation of primary hyperparathyroidism with osteoporosis, hypercalcemia, and normal parathyroid hormone level. *South Med J* 94, 339-41 (2001)

120. A.N. Hollenberg and A. Arnold: Hypercalcemia with low-normal serum intact PTH: a novel presentation of primary hyperparathyroidism. *Am J Med* 91, 547-8 (1991)

121. R. Kitazawa, S. Kitazawa, M. Fucase, T. Fujita, A. Kobayashi, K. Chihara and S. Maeda: The expression of parathyroid hormone-related protein (PTHrP) in normal parathyroid : histochemistry and *in situ* hybridation. *Histochemistry* 98, 211-215 (1992)

122. H. Matsushita, M. Hara, H. Nakazawa, Y. Shishiba and T. Matuhasi: The presence of immunoreactive parathyroid hormone-related protein in parathyroid hormone-relatd protein in parathyroid adenoma cells. *Acta Pathol Jpn* 42, 35-41 (1992)

123. F.R. Bringhurst, M.B. DeMay and H.M. Kronenberg: Hormones and disorders of mineral metabolism In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, eds. *Williams Textbook of Endocrinology*. 10th ed. Philadelphia, Pa: Saunders, 1303–1372 (2003)

124. J.W. Suliburk and N.D. Perrier: Primary hyperparathyroidism. *Oncologist* 12, 644-53 (2007)

125. R.A. DeLellis, P. Mazzaglia and S. Mangray: Primary hyperparathyroidism: a current perspective. *Arch Pathol Lab Med* 132, 1251-62 (2008)

126. A. Mithal, F. Bandeira, X. Meng and D.S. Rao: Clinical presentation of primary hyperparathyroidism in India, Brazil and China. In: JP Bilezeikian, MA Levine, R Marcus eds. *The Parathyroid Academic Press*, San Diego, CA, 375-86 (2001)

127. S.J. Silverberg: Diagnosis, natural history, and treatment of primary hyperparathyroidism. *Cancer Treatment and Research* 89,163-81 (1997)

128. S.E. Rodgers, J.I. Lew and C.C. Solorzano: Primary hyperparathyroidism. *Curr Opin Oncol* 20, 52-8 (2008)

129. A.G. Kettle and M.J. O'Doherty: Parathyroid imaging: how good is it and how should it be done? *Semin Nucl Med* 36, 206-11 (2006)

130. C.N. Foroulis, S. Rousogiannis, C. Lioupis, D. Koutarels, G. Kassi and A. Lioupis: Ectopic paraesophageal mediastinal parathyroid adenoma, a rare cause of acute pancreatitis. *World J Surg Oncol* 30, 2:41 (2004)

131. S. Adamek, P. Libansky, O. Nanka, J. Sedy and P. Pafko: Surgical therapy of primaryhyperparathyroidism and its complications. Experience with 453 patients. *Zentralbl Chir* 130, 109-13 (2005)

132. B. Castleman and S.I. Roth: Tumors of the parathyroid glands. In Atlas of Tumor Pathology, Washington, DC, *Armed Forces Institute of Pathology*, series 2, fascicle 14 (1978)

133. H.R. Wolpert, A.L. Vickery Jr and C.A. Wang: Functioning oxyphil cell adenomas of the parathyroid gland. A study of 15 cases. *Am J Surg Pathol* 13, 500-4 (1989)

134. B.S. Bleier, V.A. LiVolsi, A.A. Chalian, P.A. Gimotty, J.D. Botbyl and R.S. Weber: Technetium Tc-99m sestamibi sensitivity in oxyphil cell-dominant parathyroid adenomas. *Arch Otolaryngol Head Neck Surg* 132, 779-82 (2006)

135. K.K. Prasad, G. Agarwal, S.K. Mishra and N. Krishnani: Oxyphilic cell adenoma of parathyroid resulting in primary hyperparathyroidism and osteitis fibrosa cystica--a case report. Indian J Pathol Microbiol 49, 448-50 (2006)

136. R. Mihai, F. Gleeson, I.D. Buley, D.E. Roskell and G.P. Sadler: Negative imaging studies for primary hyperparathyroidism are unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. World J Surg 30, 697-704 (2006)

137. N.Y. Mehta, J.M. Ruda, S. Kapadia, P.J. Boyer, C.S. Hollenbeak and B.C. Stack Jr.: Relationship of technetium Tc 99m sestamibi scans to histopathological features of hyperfunctioning parathyroid tissue. Arch Otolaryngol Head Neck Surg 131, 493-8 (2005)

138. J. Fleischer, C. Becker, D. Hamele-Bena, T.L. Breen and S.J. Silverberg: Oxyphil parathyroid adenoma: a malignant presentation of a benign disease. J Clin Endocrinol Metab 89, 5948-51 (2004)

139. W. Zhou, M.H. Katz, L.J. Deftos, C.S. Snyder, S. Baird and M. Bouve: Metachronous double parathyroid adenomas involving two different cell types: chief cell and oxyphil cell. Endocr Pract 9, 522-5 (2003)

140. M. Melloul, A. Paz, R. Koren, S. Cytron, R. Feinmesser and R. Gal: 99mTc- MIBI scintigraphy of parathyroid adenomas and its relation to tumour size and oxyphil cell abundance. *Eur J Nucl Med* 28, 209-13 (2001)

141. N.K. Dewanda, S. Chumber, N. Tandon and A.K. Karak: Functioning oxyphil adenoma of parathyroid. *J Postgrad Med* 46, 215-6 (2000)

142. A. Pinero, J.M. Rodriguez, S. Ortiz, T. Soria, J. Bermejo, M.A. Claver, M. Canteras and P. Parrilla: Relation of biochemical, cytologic, and morphologic parameters to the result of gammagraphy with technetium 99m sestamibi in primary hyperparathyroidism. *Otolaryngol Head Neck Surg* 122, 851-5 (2000)

143. A. Carpentier, S. Jeannotte, J. Verreault, B. Lefebvre, G. Bisson, C.J. Mongeau and P. Maheux: Preoperative localization of parathyroid lesions in hyperparathyroidism: relationship between technetium-99m-MIBI uptake and oxyphil cell content. *J Nucl Med* 39, 1441-4 (1998)

144. E. Lundgren, P. Ridefelt, G. Akerstrom, S. Ljunghall and J. Rastad: Parathyroid tissue in normocalcemic and hypercalcemic primary hyperparathyroidism recruited by health screening. *World J Surg* 20, 727-34 (1996)

145. K. Natsui, K. Tanaka, M. Suda, A. Yasoda, C. Shigeno, J. Konishi and K.Nakao: Oxyphil parathyroid adenoma associated with primary hyperparathyroidism and marked post-operative hungry bone syndrome. *Intern Med* 35, 545-9 (1996)

146. A.S. Soin, S. Gupta, N. Kochupillai and L.K. Sharma: Primary hyperparathyroidism--an Indian study. *Indian J Cancer* 31, 72-7 (1994)

147. D. Sandrock, M.J. Merino, J.A. Norton and R.D. Neumann: Ultrastructural histology correlates with results of thallium-201/technetium-99m parathyroid subtraction scintigraphy. *J Nucl Med* 34, 24-9 (1993)

148. T. Shimada, K. Higashi, K. Kimura, T. Shido and K. Miura: A case of primary hyperparathyroidism due to an oxyphil cell adenoma. *Endocrinol Jpn* 39, 499-505 (1992)

149. T. Yoshihara, M. Morita, T. Masuda, T. Kanda and S.Takemiya: Parathyroid gland adenoma in primary hyperparathyroidism: report of two cases--chief and oxyphil cell adenoma. *Auris Nasus Larynx* 18, 189-97 (1991)

150. M. Gomez Morales, M. Munoz Torres, P.L. Fernandez and F. Escobar: Oxyphil cell adenoma and primary hyperparathyroidism. *Rev Clin Esp* 187, 202-3 (1990)

151. C.D. Bedetti, A. Dekker and C.G. Watson: Functioning oxyphil cell adenoma of the parathyroid gland: a clinicopathologic study of ten patients with hyperparathyroidism. *Hum Pathol* 15, 1121-6 (1984)

152. F.H. Rodriguez Jr., D.P. Sarma, J.H. Lunseth and J.M. Guileyardo: Primary hyperparathyroidism due to an oxyphil cell adenoma. *Am J Clin Pathol* 80, 878-80 (1983)

153. N.G. Ordonez, M.L. Ibanez, B. Mackay, N.A. Samaan and R.C. Hickey: Functioning oxyphil cell adenomas of parathyroid gland: immunoperoxidase evidence of hormonal activity in oxyphil cells. *Am J Clin Pathol* 78, 681-9 (1982)

154. G.V. Poole Jr, D.A. Albertson, R.B. Marshall and R.T. Myers: Oxyphil cell adenoma and hyperparathyroidism. *Surgery* 92, 799-805 (1982)

155. L.J. Valenta, H. Eisenberg, A. Fishman, A.N. Elias, F. Pezzlo and M. Gordon: Hyperparathyroidism due to a cystic parathyroid adenoma after irradiation of the neck. *Clin Endocrinol (Oxf)* 17, 123-8 (1982)

156. S.H. Jone and P. Dietler: Oxyphil cell adenoma as a cause of hyperparathyroidism. *Am J Surg* 141, 744-5 (1981)

157. T.B. Allen and K.M. Thorburn: The oxyphil cell ij abnormal parathyroid glands. A Study of 114 cases. *Arch Pathol Lab Med* 105, 421-7 (1981)

158. R. Sandler, L.M. Jourdan and I. Damjanov: Functioning oxyphil parathyroid adenoma. *Ann Clin Lab Sci* 11, 180-3 (1981)

159. D.H. McGregor, L.G. Lotuaco, M.S. Rao and L.L.H. Chu: Functioning oxyphilic adenoma of parathyroid gland: an ultrastructural and biochemical study. *Am J Patol* 92, 691-712 (1978)

160. B. Webber: Oxyphil adenoma of the parathyroid gland. *S Afr J Surg* 13, 115-7 (1975)

161. K.F. Wellmann: Oxyphil cell adenomas associated with primary hyperparathyroidism. *Dtsch Med Wochenschr* 16, 1127-32 (1975)

162. B.M. Arnold, K. Kovacs, E. Horvath, T.M. Murray and H.P. Higgins: Functioning oxyphil cell adenoma of the parathyroid gland: evidence for parathyroid secretory activity of oxyphil cells. *J Clin Endocrinol Metab* 38, 458-62 (1974)

163. L. Ananthakrishnan, P.M. Ratnasabaoathy, R. Natanasabapathy, A.R. Balakrishnan and A.S. Ramakrishnan: A case of functioning oxyphil cell adenoma of the parathyroid gland. *Am Surg* 37, 369-70 (1971)

164. H.M. Selzman and R.E. Fechner: Oxyphil adenoma and primary hyperparathyroidism. Clinical and ultrastructral observations. *JAMA* 199, 359-61 (1967)

165. S.R. Nussbaum, R.J. Zahradnik, J.R. Lavigne, G.L. Brennan, K. Nozawa-Ung, L.Y. Kim, H.T. Keutmann, C.A. Wang, J.T. Potts and G.V. Segre: Highly sensitive two-site immunoradiometric assay for parathyrin, and its clinical utility in evaluating patients with hypercalcemia. *Clinical Chemistry* 33, 1364-1367 (1987)

166. S.R. Nussbaum and J.T. Potts Jr.: Immunoassay for parathyroid hormone 1-84 in the diagnosis of hyperparathyroidism. *J Bone Min Res* 6, S43-S50 (1991)

167. S.J. Silverberg, P. Gao, I. Brown, P. Logerfo, T.L. Cantor and J.P. Bilezikian: Clinical utility of an immunoradiometric assay for parathyroid hormone (1-84) in primary hyperaparathyroidism. *J Clin Endocrinol Metab* 88, 4725-4730 (2003)

168. S.K. Bhadada, M. Cardenas, A. Bhansali, B.R. Mittal, A. Behera, G.V. Chanukya, U. Nahar and D.S. Rao: Very low or undetectable intact parathyroid hormone levels in patients with surgically verified parathyroid adenomas. *Clin Endocrinol (Oxf)* 69, 382-5 (2008)

169. A. Gurrado, A. Marzullo, G. Lissidini, A. Lippolis, D. Rubini, G. Lastilla and M. Testini: Substernal oxyphil parathyroid adenoma producing PTHrP with hypercalcemia and normal PTH level. *World J Surg Oncol* 6: 24 (2008)

170. T.K. Khoo, C.H. Baker, H.S. Abu-Lebdeh and R.A. Wermers: Suppressibility of parathyroid hormone in primary hyperparathyroidism. *Endocr Pract* 13, 785-9 (2007)

171. F.W. Lafferty, C.R. Hamlin, K.R. Corrado, A. Arnold and J.M. Shuck: Primary hyperparathyroidism with a low-normal, atypical serum parathyroid hormone as shown by discordant immunoassay curves. *J Clin Endocrinol Metab* 91, 3826-9 (2006)

172. M.J. Bundgaard, E. Kvist and B. Kristensen: Primary hyperparathyroidism with serum parathyroid hormone within the normal range. *Ugeskr Laeger* 162, 4937-8 (2000)

173. W. Marcinkowski, T. Nieszporek, F. Kokot, A. Podwinski, A. Niemiec and M. Wieczorek: Clinical and biochemical picture of primary hyperparathyroidism based on 155 observed cases. *Pol Arch Med Wewn* 103, 1-6 (2000)

174. C. Mischis-Troussard, P. Goudet, B. Verges, P. Cougard, C. Tavernier and J.F. Maillefert: Primary hyperparathyroidism with normal serum intact parathyroid hormone levels. *QJM* 93, 365-7 (2000)

175. D.C. Baugmart, M. Ventz and W. Wermke: 18-year-old patient with hypercalcemia, hypophosphatemia, nephrocalcinosis and normal iPTH values. *Internist (Berl)* 39, 403-8 (1998)

176. L. Haddock, F. Aguilo Jr, E. Vazquez Quintana, M.C. Vazquez, V. Rabell and M. Allende: Clinical profile of 128 subjects operated for primari hyperparathyroidism. *P R Health Sci J* 17, 309-16 (1998)

177. R. Okazaki, T. Mtsumoto, Y. Furukawa, Y. Fujimoto, H. Niimi, Y. Seino, T. Fujita, S. Nagataki and E. Ogata: Serum intact parathyroid hormone concentration measured by a two-site immunoradiometric assay in normal subjects and patients with various parathyroid disorders. *Endocrinol Jpn* 39, 115-20 (1992)

178. A. Bergenfelz, S. Valdermarsson and B. Ahren: Measurement of intact parathyroid hormone in the diagnosis of hyperparathyroidism. *Acta Endocrinol (Copenh)* 125, 668-74 (1991)

179. T.A. Broughan, M.T. Jaroch and C.B. Esselstyn Jr.: Parathyroid hormone assay. Unreliable and overused. *Arch Surg* 121, 841-2 (1986)

180. J. Coetzee, L.J. Klaff and S. Epstein: Measurement of human serum parathyroid hormone in disorders of calcium metabolism and during administration of certain gut hormones. *S Afr Med J* 57, 165-70 (1980)

181. H.V. Setton and H.S. Jupperman: Normal parathormone level with primary hyperparathyroidism; clinical profile. *N Y State J Med* 79, 2071-2 (1979)

182. J.C. Hammonds, J.L. Williams and L. Harvey: Primary Hyperparathyroidism: a review of cases in the Sheffield area. *Br J Urol* 48, 539-48 (1976)

183. Y. Kinoshita, M. Taguchi, A. Takeshita, D. Miura, S. Tomikawa and Y. Takeuchi: 1,25-Dihydroxy vitamin D suppresses circulating levels of parathyroid hormone in a patient with primary hyperparathyroidism and coexistent sarcoidosis. *Journal of Clinical Endocrinology and Metabolism* 90, 6727-31 (2005)

184. R.K. Rude: Magnesium deficiency in parathyroid function. In: JP Bilzekian, R Marcus, MA Levin eds. *The Parathyroids*. Raven Press, New York, 763-77 (2001)

185. J. Tate and G. Ward: Interferences in immunoassay. *The Clinical Biochemist Reviews* 25, 105-20 (2004)

186. R. Leboeuf, M.F. Langlois, M. Martin, C.E. Ahnadi and G.D. Fink: « Hook effect » in calcitonin immunoradiometric assay in patients with metastatic medullary thyroid carcinoma : case report and review of the literature. *Journal of Clinical Endocrinology and Metabolism* 91, 361-64 (2006)

187. H. Matsushita, M. Usui, M. Hara, Y. Shishiba, H. Nakazawa, K. Honda, K. Torigoe, K. Kohno and M. Kurimoto: Co-secretion of parathyroid hormone and parathyroid-hormone-related protein via a regulated pathway in human parathyroid adenoma cells. *Am J Pathol* 150, 861-71 (1997)

188. H.M. Docherty, W.A. Ratcliffe, D.A. Heath and K. Docherty: Expression of parathyroid hormone-related protein in abnormal human parathyroids. *J Endocrinol* 129, 431-8 (1991)

189. J.A. Danks, P.R. Ebelin, J.A. Hayman, H. Diefenbach-Jagger, F.M. Collier, V. Grill, J. Southby, J.M. Moseley, S.T. Chou and T.J. Martin: Immunohistochemical localization of parathyroid hormone-related protein in parathyroid adenoma and hyperplasia. *J Pathol* 161, 27-33 (1990)

190. B. Turgut, S. Elagoz, T. Erselcan, A. Koyuncu, H.S. Dokmetas, Z. Hasbek, S. Ozdemir and C. Aydin: Preoperative localization of parathyroid adenomas with technetium-99m methoxyisobutylisonitrile imaging: relationship with P-glycoprotein expression, oxyphilic cell content, and tumoral tissue volume. *Cancer Biother Radiopharm* 21, 579-90 (2006)

191. S. Takebayashi, H. Hidai, T. Chiba, Y. Takagi, Y. Nagatani and S. Matsubara: Hyperfucntional parathyroid glands with 99mTc-MIBI scan: semiquantitative analysis correlated with histological findings. *J Nucl Med* 40, 1792-7 (1999)

192. M. Ishibashi, H. Nishida, H.W. Strauss, K. Kojima, H. Fujito, J. Watanabe, Y. Hiromatsu and N. Hayabuchi: Localization of parathyroid glands using technetium-99m-tetrofosmin imaging. *J Nucl Med* 38, 706-11 (1997)

193. Y. Erbil, Y. Kapran, H. Issever, U. Barbaros, I. Adalet, F. Dizdaroglu, A. Bozbora, S. Ozarmagan and S. Tezelman: The positive effect of adenoma weight and oxyphil cell content on preoperative localization with 99mTc-sestamibi scanning for primary hyperparathyroidism. *Am J Surg* 195, 34-9 (2008)

194. A.E. Stephen, S.I. Roth, D.W. Fardo, D.M. Finkelstein, G.W. Randolph, R.D. Gaz and R.A. Hodin: Predictors of an accurate preoperative sestamibi scan for single-gland parathyroid adenomas. *Arch Surg* 142, 381-6 (2007)

195. R.W. Westreich, M. Brandwein, J.I. Mechanick, D.A. Bergman and M.L. Urken: Preoperative parathyroid localization: correlating false-negative technetium 99m sestamibi scans with parathyroid disease. *Laryngoscope* 113, 567-72 (2003)

Abbreviations: PTHrP: parathyroid hormone-related peptide; HHM: humoral hypercalcemia of malignancy; PTH1R: PTH type 1 Receptor; PTH: parathyroid hormone; PHPT: primary hyperparathyroidism; cAMP: cyclic adenosine monophosphate; AC/PKA: adenylyl cyclase/protein kinase A; PLC/PKC: phospholipase C/protein kinase C; 1,24 (OH)2D3: 1,24-dihydroxyvitamin D3; IRMA: immunoradiometric assay; ICMA: immunochemiluminescent assay; mRNA: messenger ribonucleic acid; Tc-99m-sestamibi: Technetium-99m sestamibi.

Key words: PTHrP, PTH, Primary Hyperparathyroidism, Hypercalcaemia, Parathyroid Adenoma, Review

Send correspondence to: Mario Testini, Unit of Endocrine Surgery, Section of General and Thoracic Surgery, Department of Applications in Surgery of Innovative Technologies, University Medical School of Bari , Policlinico, P.zza G. Cesare 70124 BARI, Italy, *Te.: 0039.080.5592882, Fax.: 0039.080.5592882* E-mail: mario.testini@chirgen2.uniba.it

http://www.bioscience.org/current/volS2.htm