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Parathyroid Hormone Related Protein in Hypercalcemia Malignancies

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ABSTRACT

Background: Paraneoplastic syndromes encompass symptoms or signs caused by malignant tumors through humoral factors, such as hormones or cytokines, produced by tumor cells. Hypercalcemia is a common occurrence in cancer patients, particularly associated with Parathyroid Hormone-related Protein (PTHrP). PTHrP mimics parathyroid hormone (PTH) activity, leading to excessive bone resorption, hypocalcemia, and significant metabolic complications.

Discussion: PTHrP plays a key role in malignancy-associated hypercalcemia, which is more acute and severe compared to primary hyperparathyroidism. PTHrP is produced by various tumors, including squamous cell carcinomas and breast adenocarcinomas, as well as some hematologic malignancies. Beyond its extracellular role in bone resorption, PTHrP also exerts intracellular effects through nuclear activities, influencing cell proliferation and apoptosis. Management of hypercalcemia prioritizes patient hydration, bisphosphonate use, and targeted therapies to mitigate PTHrP effects. Emerging treatments, such as monoclonal antibodies against PTHrP and osteoprotegerin, show potential for rapid calcium control.

Conclusion: PTHrP is a critical biomarker in malignancy-associated hypercalcemia, reflecting its central role in calcium metabolism regulation and as a promising target for innovative therapies. Prompt management of this condition can enhance patients' quality of life and reduce the risk of severe complications.

Keywords: Paraneoplastic syndrome, hypercalcemia, parathyroid hormone-related protein (PTHrP)

1 Introduction

Paraneoplastic syndrome refers to symptoms or signs resulting from damage to organs or tissues distant from primary malignancy or its metastases. These syndromes can affect multiple organs and tissues, deriving their name from Greek roots "para" (beside or near), "neo" (new), and "plastic" (formed), meaning "beside new formation, or cancer." Broadly, paraneoplastic syndromes are clusters of symptoms caused by substances produced by tumor cells. They may involve endocrine, neuromuscular, cardiovascular, dermatological, hematological, gastrointestinal, renal, or other organ systems [1,2].

Paraneoplastic syndromes can occur in any malignancy, with a prevalence of approximately 8% among cancer patients. One notable endocrine manifestation is hypercalcemia, often associated with malignancy. Hypercalcemia presents with a wide range of symptoms, including fatigue, depression, altered

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consciousness, anorexia, nausea, vomiting, constipation, reversible renal tubular defects, polyuria, and short QT intervals on electrocardiograms. Severe cases may involve cardiac arrhythmias [3]. Clinically, hypercalcemia becomes symptomatic at serum calcium levels exceeding 2.9–3.0 mmol/L (11.6–12.0 mg/dL). Levels above 3.2 mmol/L (12.8 mg/dL) can lead to calcification in kidneys, vessels, lungs, and other organs, potentially causing renal insufficiency. Extreme hypercalcemia (≥3.7–4.5 mmol/L or 14.8–18.0 mg/dL) constitutes a medical emergency, risking coma and cardiac arrest [3].

Approximately 20% of cancer patients experience hypercalcemia during their disease course. Malignancy-induced hypercalcemia, often linked to Parathyroid Hormone-related Protein (PTHrP), indicates poor prognosis and requires urgent management due to high morbidity and mortality. Compared to primary hyperparathyroidism, malignancy-induced hypercalcemia is more acute and severe. It is frequently accompanied by hypophosphatemia, reduced tubular phosphorus reabsorption, increased tubular calcium reabsorption, and elevated nephrogenous cyclic AMP, reflecting PTHrP's role in mimicking parathyroid hormone activity [4,5].

2 Parathyroid Hormone Related Protein (PTHrP)

Parathyroid Hormone-Related Protein (PTHrP) and its gene (PTHLH) were identified approximately 25 years ago, marking a significant breakthrough in understanding pathophysiology of hypercalcemia in malignancy. Initially described by Fuller Albright in 1941, PTHrP mimics parathyroid hormone (PTH), contributing to bone resorption and hypercalcemia through same receptor, PTH1R. Its discovery clarified mechanisms behind humoral hypercalcemia of malignancy (HHM) but left questions about its physiological role in normal tissues [5]. PTHrP is encoded by a single gene on chromosome 12. Alternative splicing generates three distinct isoforms of 139, 141, and 173 amino acids. These isoforms share structural homology with PTH, allowing both to bind and activate PTH1R. This interaction explains hypercalcemic effects seen in malignancy. PTHLH gene has a complex organization with three promoters and at least seven exons, enabling diverse expression patterns [6].

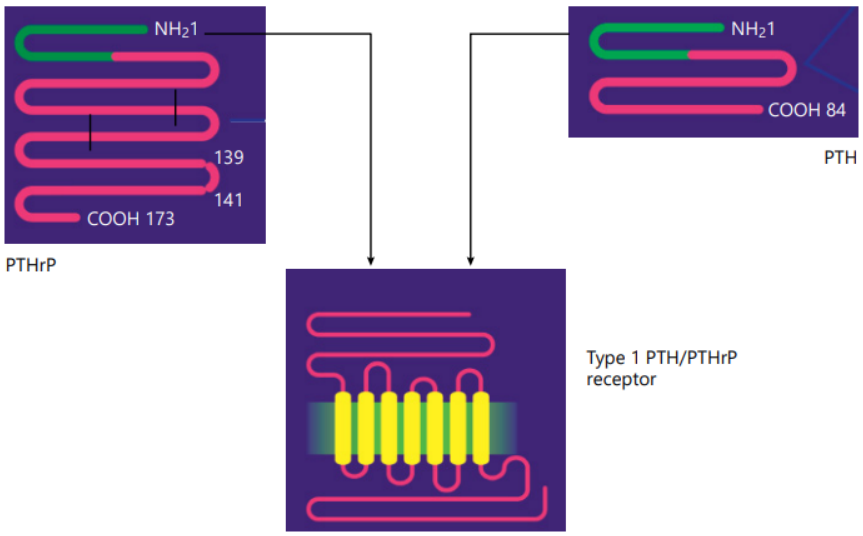

Figure 1. Human PTHrP translated into 3 forms from 139, 141, and 173 amino acids.[3]

PTHrP is most common cause of malignancy-associated hypercalcemia and can induce hypercalcemia and hypophosphatemia even in absence of bone metastases. It is secreted by a variety of cell types, including keratinocytes and mammary epilial cells. Growth factors like EGF, IGF-1, and TGF-β stimulate PTHLH transcription, while hormones such as 1,25(OH)2D and glucocorticoids inhibit its expression [7]. Despite extensive research, cell-specific processing of PTHrP and biological significance of its overlapping peptides remain incompletely understood. PTHrP plays critical roles in both endocrine and paracrine signaling, underlining its importance in malignancy-related complications and normal tissue physiology.

Amino-terminal sequence of PTHrP shares significant homology with PTH, with 8 of the first 13 amino acids being identical. This similarity enables both PTHrP(1–36) and PTH(1–34) to bind and activate common PTH1R receptor, a G-protein-coupled receptor (GPCR) that regulates calcium and phosphate homeostasis. In addition to its extracellular signaling role, PTHrP contains a functional bipartite nuclear localization signal (NLS) within residues 87–106, facilitating its nuclear entry and intranuclear activity. Inside nucleus, PTHrP modulates cell proliferation and apoptosis, with knock-in mice lacking NLS domain showing growth retardation, organ defects, and early apoptosis [8].

PTHrP is widely expressed in fetal and adult tissues, contrasting with parathyroid-exclusive expression of PTH. It plays crucial roles in skeletal development, particularly in chondrocyte proliferation and endochondral ossification. Absence of PTHrP leads to reduced chondrocyte proliferation and accelerated differentiation, resulting in skeletal defects. In animal models, PTHrP acts synergistically in paracrine and intracrine pathways to regulate bone growth and osteoblast activity, with deficiencies leading to diminished trabecular bone density and osteoblast function [9].

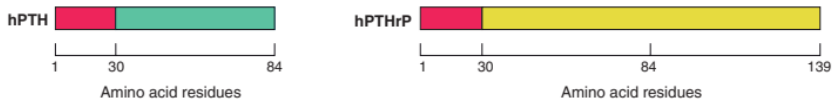

Figure 2. Amino acids structure of PTH and PTHrP.[9]

While PTH predominates in adult calcium homeostasis, PTHrP becomes clinically significant in malignancy-associated hypercalcemia. Tumor-driven PTHrP overproduction mirrors PTH activity, disrupting bone density, kidney function, and calcium balance, often with suppressed serum PTH levels. Mechanistically, PTHrP overproduction is linked to promoter demethylation and gene amplification, driven by tumor growth factors and oncogenic pathways [10,11].

PTHrP interacts with PTH1R via its C-terminal residues binding to extracellular domain (ECD) of receptor, while its N-terminal residues engage transmembrane domain to initiate downstream signaling. This activates cAMP/protein kinase A pathways and intracellular calcium transients, aligning its function with other GPCRs in class B. PTHrP's dual extracellular and nuclear roles underscore its importance in physiology and pathology, particularly in cancer-related hypercalcemia [11].

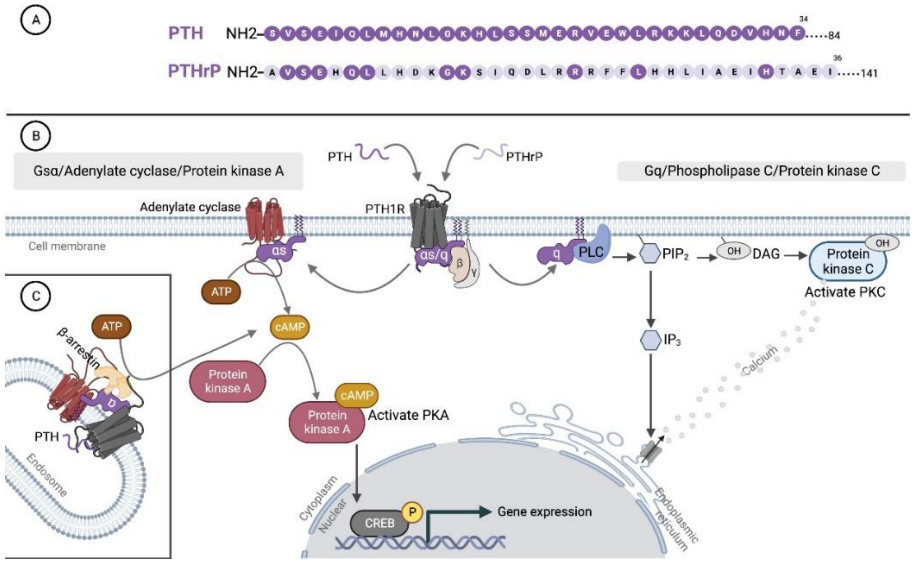

Figure 3. PTH, PTHrP, and PTH-1-receptor.[12]

Initially, PTH and PTHrP were thought to bind and activate PTHR-1 identically. However, studies reveal that PTH is more effective than PTHrP in elevating circulating calcium and 1,25-$(OH)_2$ vitamin D levels. Recent biochemical and biophysical data demonstrate that PTH and PTHrP interact differently with PTHR-1, leading to distinct temporal downstream signaling patterns. PTH stabilizes G0 conformational state of PTHR-1, enabling prolonged G protein activation and sustained cAMP production. In contrast, PTHrP favors a more transient RG conformational state, resulting in shorter signaling duration [13].

Three-dimensional crystal structures of PTH (1–34) and PTHrP (1–36) bound to extracellular domain (ECD) of PTHR-1 reveal that PTH binds more tightly to active receptor. Both peptides form amphipathic helices (amino acids 14–30) that interact with a specific cleft in receptor's ECD, but PTH's slightly longer helix provides stronger binding affinity [14].

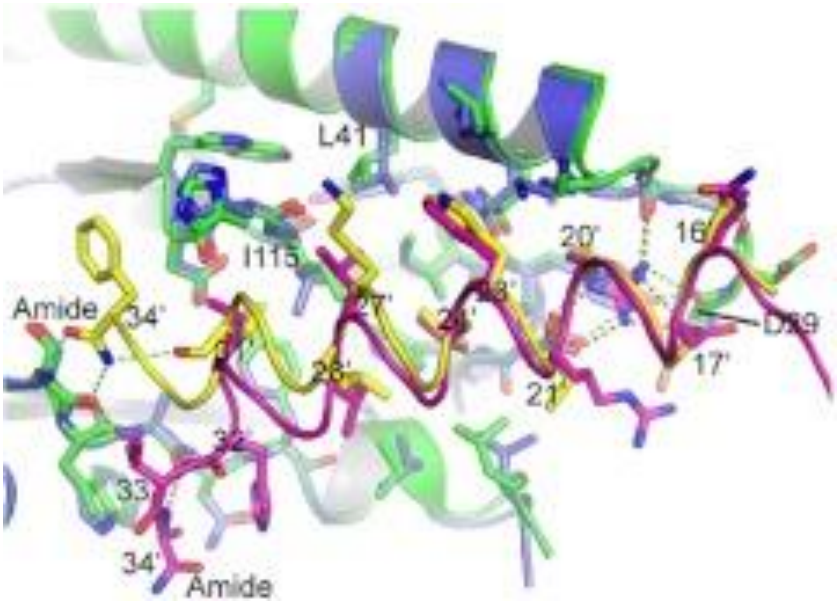

Figure 4. Three-dimensional of PTHrp (magenta) and PTH (yellow) that binds extracelluar domain from PTHR-1.[13]

PTHLH transcription can bypass signal peptide, allowing PTHrP to remain intracellular. PTHrP shuttles between cytoplasm and nucleus, mediated by a classical nuclear localization sequence (NLS) within residues 84–93. This process is regulated by cell cycle-dependent phosphorylation at Thr85 by p34cdc2 kinase.

PTHrP also binds its receptor on cell surface and is transported to nucleus upon internalization, enabling both paracrine signaling and autonomous intracellular activity. Within nucleus, PTHrP interacts with RNA, suggesting roles in RNA exchange, ribosomal dynamics, and protein translation. These dual extracellular and nuclear actions highlight PTHrP's complexity in cell signaling and regulation [15,16].

3 PTHrP and Hypercalcemia Malignancies

A thorough history and physical examination are crucial for identifying underlying cause of hypercalcemia. Reviewing previous laboratory data provides insights into baseline calcium levels and duration of hypercalcemia. A systematic evaluation of medication history (prescription and over-the-counter drugs, supplements), dietary habits, family history, and prior granulomatous diseases is essential [14,15].

Initial laboratory tests should include parathyroid hormone (PTH) levels to distinguish between PTH-mediated and non-PTH-mediated hypercalcemia. PTH-mediated hypercalcemia is associated with primary hyperparathyroidism or familial hyperparathyroid syndromes, while non-PTH-mediated hypercalcemia is linked to malignancies, granulomatous diseases, endocrine disorders, or vitamin D intoxication [15].

Familial hypocalciuric hypercalcemia (FHH) should be suspected in patients with minimally elevated PTH levels and low urinary calcium excretion. Low or normal PTH levels (<20 pg/mL) indicate non-PTH-mediated causes, warranting further evaluation of PTHrP and vitamin D metabolites. Elevated 25-hydroxyvitamin D suggests vitamin D toxicity, while increased 1,25-dihydroxyvitamin D is indicative of lymphoma or granulomatous diseases. Elevated PTHrP levels strongly suggest malignancy-associated hypercalcemia [16].

PTHrP is cleaved into N-terminal (1–86) and C-terminal peptides. Advanced assays, including C-terminal PTHrP radioimmunoassays, are currently available but may yield false positives in cases of renal impairment, as reduced kidney function can elevate PTHrP levels. Accurate interpretation requires clinical correlation [17].

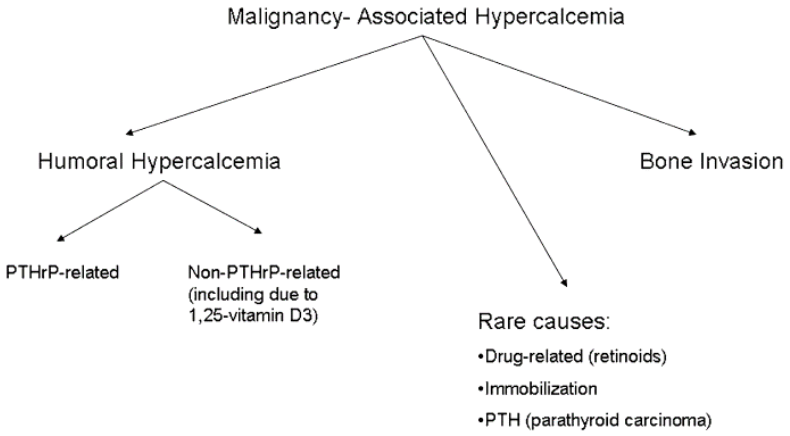

Figure 5. Hypercalcemia in maligancies.[17]

3.1 Role of PTHrP in Hypercalcemia Malignancies

Hypercalcemia in malignancy is more acute and severe compared to primary hyperparathyroidism, often accompanied by hypophosphatemia, decreased tubular phosphate reabsorption, increased calcium reabsorption, and elevated nephrogenous cAMP, reflecting actions of PTHrP. In malignancy-related hypercalcemia, osteoclastic bone resorption increases significantly, unlike osteoblastic bone formation seen in primary hyperparathyroidism. This resorption may result from factors released by tumor or bone microenvironment or from extremely high calcium levels themselves [18].

PTHrP is a key marker in malignancy-associated hypercalcemia, with elevated levels indicating cancer-related hypercalcemia. PTHrP, produced by a wide range of tumors, does not decrease after treatment of hypercalcemia but can decline as tumor shrinks. PTHrP is often elevated in normocalcemic cancer patients, suggesting its potential as a tumor marker or a predictor of impending hypercalcemia [18].

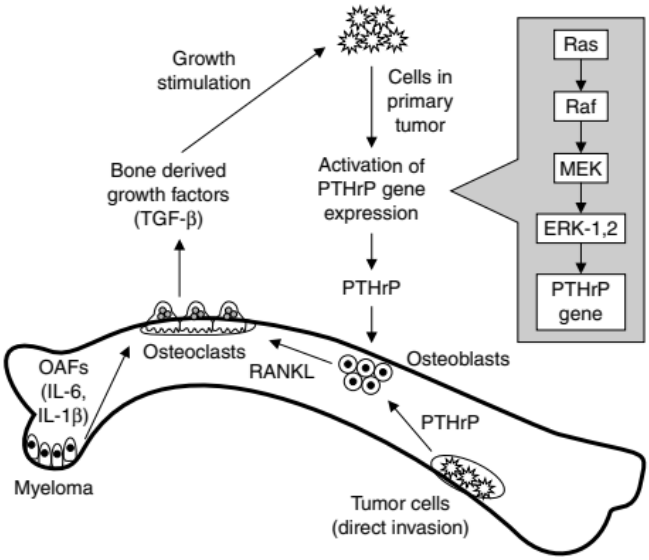

Figure 6. Pathophysiology of PTHrP in hypercalcemia malignancies.[18]

PTHrP is most commonly produced by solid tumors, particularly squamous cell carcinomas in various sites (lungs, esophagus, cervix, vulva, skin, and head/neck), and is also seen in adenocarcinomas of breast, kidney, bladder, and ovary. Conversely, cancers such as colorectal, stomach, prostate, thyroid, and non-squamous lung cancers rarely present with hypercalcemia [19]. Recent studies have shown that elevated PTHrP levels correlate with hypercalcemia, particularly in breast cancer, which is more commonly associated with osteolytic bone metastases. Hematological malignancies, such as non-Hodgkin lymphoma, chronic myeloid leukemia, and adult T-cell leukemia/lymphoma, can also produce PTHrP, though less frequently than solid tumors [18-19]. PTHrP may promote cancer growth and metastasis through paracrine, autocrine, and intracrine mechanisms, modulating tumor cell proliferation, apoptosis resistance, and enhancing tumor spread. Tumor metastases to bone can trigger PTHrP release into bone microenvironment, where it interacts with osteoblasts and osteoclasts to stimulate bone resorption and release of growth factors like IGF-1 and TGF-β. This creates a positive feedback loop that supports tumor growth and bone destruction. PTHrP's role in metastasis includes promoting angiogenesis and supporting osteolytic lesion formation. Through interactions with RANKL, PTHrP enhances osteoclastic activity, releasing calcium and facilitating further tumor cell proliferation, thereby advancing metastatic process [19].

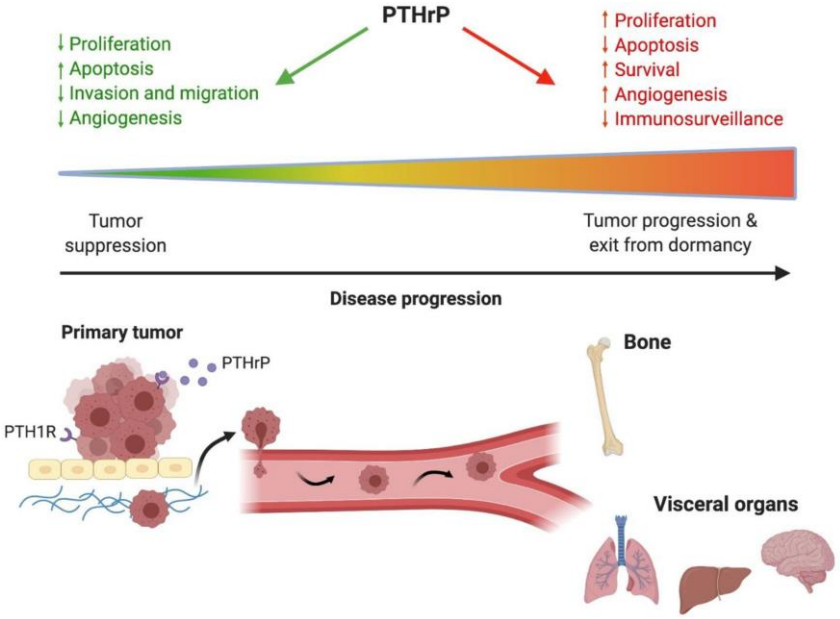

Figure 7. Role of PTHrP in tumor progression.[18]

3.2 Treatment

Main goals of treating hypercalcemia in malignancy are: (i) restoring patient's hydration status to euvolemia, (ii) normalizing serum calcium levels, and (iii) addressing the underlying cause if possible. Hypercalcemia in malignancy is often undiagnosed and inadequately managed, leading to symptoms that can significantly impact quality of life. Normalizing calcium levels can alleviate these symptoms [19].

Initial Management

First step in treatment is fluid resuscitation, as patients with symptomatic hypercalcemia often present with dehydration. Intravenous saline (2-6 liters) is used to promote calcium excretion, with loop diuretics added to enhance this effect, particularly in patients with cardiac dysfunction. Fluid intake should be carefully monitored to avoid overhydration in patients who are adequately rehydrated [20].

Goal of the treatment is to reduce serum calcium to <2.8 mmol/L (11.0 mg/dL), where most patients become asymptomatic. Symptom improvement correlates with calcium reduction, and about 70% of patients achieving normal calcium levels can be discharged from the hospital. Primary cause of hypercalcemia in malignancy is calcium release from bone. In most cases, hypercalcemia can be controlled by inhibiting osteoclast activity, highlighting osteoclast-mediated bone resorption as main cause of hypercalcemia [21].

Previous Therapies

Mithramycin, once a primary treatment, is now rarely used due to hematologic toxicity. Parenteral phosphate infusion can cause calcium deposits in tissues like kidneys, worsening renal function. Calcitonin, a direct osteoclast inhibitor, is used as an initial therapy to reduce calcium, especially within first 24 hours, but its long-term use is limited by tachyphylaxis [21].

Current Therapy: Bisphosphonates

Bisphosphonates are the most effective osteoclast inhibitors for controlling calcium levels in malignancy-associated hypercalcemia. They are absorbed into bone and inhibit osteoclast activity, with effects becoming evident after several days. Bisphosphonates like zoledronate also show potential anti-tumor and anti-angiogenic properties, which may help delay or prevent bone metastasis, though this has not yet been confirmed in humans. However, bisphosphonates can cause renal toxicity, particularly in patients with preexisting renal dysfunction, and should be used cautiously in these cases [21].

Emerging Therapies

Several new treatment approaches are being explored. One limitation of bisphosphonates is their delayed onset of action. Monoclonal antibodies targeting PTHrP, which inhibit PTHrP-mediated bone resorption, have shown rapid calcium reduction in animal models and are being evaluated for their potential in humans. Combined with bisphosphonates, these antibodies may provide a faster and more effective treatment for hypercalcemia [22]. Additionally, osteoclast activation can be inhibited using osteoprotegerin (OPG), a soluble receptor form that binds RANK-ligand. OPG has shown effectiveness in inhibiting osteoclast activity with a faster onset compared to bisphosphonates, making it a promising therapeutic option for diseases involving excessive osteoclast activity [22,23].

4 Conclusions

Paraneoplastic syndrome refers to diseases or symptoms caused by cancer, not by direct tumor invasion. It results from humoral immune factors (hormones or cytokines) secreted by tumor cells or immune responses triggered by tumor. Hypercalcemia is commonly seen in lung cancer, multiple myeloma, and renal cell carcinoma, often due to ectopic PTHrP production by tumor cells. PTHrP mimics PTH, causing excessive bone resorption and hypercalcemia. PTHrP gene, located on chromosome 12, produces multiple isoforms via alternative splicing. PTHrP is cleaved into N-terminal (1-86) and C-terminal peptides, with ongoing efforts to develop tests targeting these fragments. Hypercalcemia is a common metabolic disorder, requiring thorough evaluation to identify the underlying cause. While PTH is expressed in parathyroid glands, PTHrP is widely expressed in various tissues, playing a role in cell growth, differentiation, and

apoptosis. Its most prominent effect is on skeletal bone growth. Hypercalcemia from PTHrP in malignancy is typically more acute and severe than in primary hyperparathyroidism.

5 Competing Interests

The authors indicate no potential conflict of interest from this article.

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