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Review Article

Hypercalcemia in Malignancy-A Review

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Abstract
Malignancy is one of the most common causes of hypercalcemia, mostly seen in cancer associated bone metastasis. A common finding usually seen in patients with advanced stage cancer is malignancy associated hypercalcemia. During the cause of the illness, hypercalcemia occurs in up to 20 to 30 % of cancer patients at any stage. The clinical manifestations of hypercalcemia vary with the level of calcium in the blood. When serum calcium level is exceeded from normal limits the sign and symptoms start to appear. Hypercalcemia of the malignant disease usually presents with significantly elevated calcium levels and, therefore, usually has severe symptoms. A number of mechanism that are accountable for the increase of hypercalcemia in malignant disease, including hemorrhagic, mediated by parathyroid hormone peptide, 1,25 Vitamin D-mediated hypercalcemia, osteolytic metastases-related hypercalcemia and parathyroid Hormone, Parathyroid hormone mediated hypercalcemia in patients with parathyroid carcinoma and extra parathyroid cancer. Analysis must comprise measurement of the above mediators of hypercalcemia, as well as history and physical examination. Administration incorporates hydration, bisphosphonates, calcitonin, denosumab, prednisone and cinacaalect in certain patients. Patients with progressed basic kidney infection and headstrong serious hypercalcemia ought to be well-thought-out for hemodialysis. Hematologists or oncologists and physician care specialists should be involved early in guiding cancer-targeted treatment options and assisting patients and their confinement in comfortable care conversations.

Keywords: Hypercalcimia, Estimation of Calcium, malegnancy patients, types of malgnancy

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INTRODUCTION

Hypercalcemia is characterized as a rise of serum calcium rate over the usual limit in blood according to the reference value used in a clinical laboratory. According to the standard definition adapted, it is either higher than 2.65 mmol/L (1) or higher than 2.6 mmol/L (2). The investigation of hypercalcemia contains a number of medical factors but primarily focuses on predominant hyperparathyroidism and malignancy hypercalcemia given the highest incidence (3). Particularly in advanced stage cancer patients it has been notices that prevalence of hypercalcemia is common. Patients with malignant hypercalcemia tend to be only few months' survival poor prognosis (4).

It is uncertain whether the subsequent occurrence of cancer was affected by a symptomatic hypercalcemia. Hamilton et al. analyzed more than 52,000 patients charts and to answer this question (3). Hypercalcemia patients were low in numbers, but their diagnosis of cancer was higher in 1 year (6.2% as compared to 3.0%). In the interpretation of the results of the study, however, the retrospective methodology should be considered.

Calcium in the Body

Calcium is important for a number of bio-chemical reactions, including bone development, muscle contractions and coagulation. Calcium is primarily ingested into the small intestine and only 10-20% of the calcium obtained is consumed, with the rest being excreted by stools. Calcium is necessary for biochemical reactions (3).

The body reserves calcium in two different compartments: in bones which are contained as the main part of calcium in hydroxyapatite salt and in plasma. In plasma serum calcium found in various forms such as ionized calcium and free ionized calcium, which is indeed a physiologically active structure that

accounts for around 45% of calcium in serum, and in 65% of calcium (3).

Calcium Related Hormones

Many hormonal systems control the absorption and metabolism of calcium. It triggers calcium-sensing cells in the parathyroid drums when the concentrations of calcium drop below 10mg/dl to induce the release of Parathyroid Hormone (PTH). Calcium is less than 7.5mg/dl while PTH release has at peak (4).

Parathyroid Hormone-Related Protein (PTHrP) knockout mice die shortly after birth from the developmental abnormalities of thoracic bones due to asphyxia (4). In most forms of cancer-induced HHM, PTHrP has been shown to be the main factor. NF-Fraktionb, TGF-den and/or Ras-MASK (5-6) are the regulators for transmission of PTHrP. In mature persons T-cell-leukemia or lymphoma (7-8) may activate the promoter of PTHrP by linking HTLV-1 oncoprotein. Cyclic adenosin monophosphates / protein kinase A and the protein C / Protein kinase C waterfall are the activities of PTHrP based on the stimulation of various indication transduction pathways. Therefore, PTHrP fragments have various functions, based on the composition of different tissues (4).

Once C-term PTHrP were temporarily introduced to osteoblastic cells, the over-expression of vascular endothelial growth factor receptor 2 (VEGFR2) via PKC / ERK activation was affecting anabolic effects (9). Bone resorption via the PTH1, which identifies para-thyroid hormone as well as PTHrP, cAMP-PKA pathways are needed to be triggered (10).

Through down-regulating Osteoprotegerin (OPG) promoters through activating the cyclic adenosine onophosphate/protein kinase A cAMP / PKA pathway (11), OPG content suppress by PTH & PTHrP. PTHrP promotes development of RANKL, on the other side, causes bone resorption. In osteoblast control, the balance between the RANKL and the OPG levels is an important factor (12).

In Adults T-cell leukemia lymphoma (ATLL), RANKL activation in patients with hypercalcemia-related tumor cells. RANKL osteoclastogenesis caused by direct contact to the precursor cells on the surface of leukemic cells (13). In the disconnection of the bone forming and resorption bone in malgninancy, specific osteoclasts activation by tumor cells may be necessary (14).

Several essential pathways are explored here for malignancy hypercalcemia. First, it is regulated by development of parathyroid related protein (PTHrP) that the key mechanism accounts for approximately 80% of malignancy-related hypercalcemia. It must also be remembered that PTHrP is usually made and secreted by different cells, especially healthy breast cells (15).

The PTHrP also acts in the growth of different tissues under ordinary psychological conditions, stimulates Tran's placental calcium delivery and encourages the conversion of calcium to breast milk. PTH and PTHrP are working in a consistent way interact with the same receptors. The biochemical composition of PTHrP, though, seems to have no major impact on 1-25,dihydroxycholecalciferol. The arrangement of the biochemical PTHrP is very close to that of postpartum hemorrhage **(**PPH) (14). The PTHrP therefore acts against osteoblasts, resulting in enhanced RANKL synthesis, with osteoblastic activation and calcium-release bone resorption in the bloodstream subsequently. Another pathway through which PTHrP induces hypercalcemia is enhanced renal calcium reabsorption. Many malignant diseases contributing to hypercalcemia by PTHrP is linked to squamous cell, urinary cancer (Kidney cancer and bladder cancer), nonhodgkin's lymphoma, ovarian cancer and breast cancer (16-18).

Hypercalcemia in Different Malignancies

High level of calcium is one of the foremost serious paraneoplastic disorders. The existence of hypercalcemia in adult T-cell leukemia /lymphoma (ATLL) is 50 to 90 %, in lung cancer prevalence is 27-35% and in breast cancer is 25-30 %. The prevalence of hypercalcemia in multiple myeloma is 7-30 % and <10 % found in further types of malignancy patients (19 -20).

Malignancy Hypercalcemia (HM) is defined by 1 flowing humoral factors originating from the tumor cells, 2 uncoupled bone development and resorption, 3 decreased reabsorption of kidney calcium even though the glomerular filtrate is triggered by hypercalciuria. By comparison with HM, bone growth and resorption are both elevated by primary hyperparathyroidism and contribute to fibrous osteodystrophy in long-standing illnesses (19).

The HM is a typical complexity of certain leukemia's; squamous cell carcinomas, breast and renal carcinomas, and some time in other tumors (21). Cancer cells secret factors which stimulate the osteoclastic bone resorption (indirectly or directly osteoblast) and increase the survival of osteoclast progenitors or adult osteoclasts.

Hypercalcemic cancer-derived conditions potentially induce osteoclastic bone resorption through the activation of osteoblastic or bone stromal osteoclastic triggers. The rise in the serum calcium level can be accounted for under normal physiological circumstances by reducing the intestinal calcium absorption, raising the excretion of kidney calcium, decrease PTH secretion and decreased the joints. The release of the PTHrP is also used to improve kidney absorption by triggering the parathyroid hormone receptor 1 (PTH1R), which stimulates the production of HHM, which enhances the absorption from the renal calcium in the kidney (22).

In some cancer cells, for example, breast and prostate tumors, CaR is also expressed (23). Nevertheless, an improvement of extracellular calcium in these cells results in increased production of PTHrP (24). Increases PTHrP induces osteoclastic resorption of the bone and reabsorption of renal calcium to contribute to HHM. PTHrP, calcium and CaR are a positive feedback loop that's special to HHM. While PTHrP transcription has been expressly disabled, CaR mutation in breast cancer has been shown to have a benefit in functions.

Specific nucleotide polymorphisms in CaR identified in human lung squqmous cell carcinoma (25). In the case of patients with lung-squamous cell carcinoma, functional analysis of the nonconserve amino acid replacement (R990 G) of CaR-inducted HHM. Breast and prostate cancer have shown dysregulation of PTHrP and HHM expression induced by CaR signalling (26).

Increased concentrations of PTHrP, IL-6, and 1.25 dihydroxy vitamin D in serum were observed in patients with large diffuse, hypercalcemic B cell lymphoma (27). These patients also experienced diffuse osteolytic lesions and nephrocalcinosis.

Patients with primary cutaneous B-cell lymphoma have been documented for hypercalcemia (28-29). One person has seen an elevated serum level of 1, 25-dihydroxy-vitamin D and untraceable PTH and PTHrP. Hypercalcemia pathogenesis has not been identified in these cases.

The TnF-Tesis has improved in vivo expression in the tumor in a xenograft mouse model of canine lymphoma (30). Bone histomorphometry has shown that the main cause of HHM in these mice is increased osteoclastic bone resorption. Increased PTHrP circulation in lymphoma and HHM cats has been reported (31) too. HHM can also be formed by cats because of unexplained moor caused by contamination with feline leukemia (32). Amazon parrot with lymphoma has also reported hypercalcemia (33).

Hypercalcemia and Immune System

One of the important ways in which NF-TB is partially stimulated in tumor cells is to rise the excretion of provocative cytokines from cancer cells, including tumor necrosis cancer factor (TNF), IL-6, IL-1, IL-8, CCL2 ,MCSF and CXCL12 (34).

Rises of osteoclastic bone resorption like rheumatoid joint pain (35), osteomyelitis, aseptic untying osteolysis syndrome and Osteoporosis (37) activated by macrophages the replacements in the articular joints, are critical factors in the pathogenesis of several inflammatory and anti-inflammation diseases (37).

Higher plasma IL-6 was observed in HHM cancer patients including multiple myeloma, squamous liver carcinoma and mature person T-cell leukaam/ lymphoma (38-39). Enhances osteoclastic recruitment by linking osteoblast receptors to the signal pathways of the STAT-1/3-and MAPK-activated protein kinase (signal) transducer and transcription-activator (STAT). The effect on osteoclast development is also strengthened by PTH and PTHrP, and inflammatory cytokine, like IL-1 and TNF-t, are regulated (40).

For variation and propagation of osteoclastic precursor (41), macrophage-colony stimulation factor (M-CSF) is important. Interferon (IFN)-Teles disrupts JAK/STAT in an osteoblast, contributing to reduce cathepsin K and tatrate responsive phosphatase (TRAP) in mature osteoclasts (42). Transgender mice also established greater osteolytic bone lesion (HLV-1) and decreased osteoclastic disease, like HTLV-1, viral oncoprotein and taxes, as well as IFN knockout. Administering IFN-tumor- inhibited malignant tumor growth and decreased hypercalcemia in mice transplanted with tax-positive tumors, indicating the defensive role of IFN-α beneficial impact for the production of HHM (42).

Treatment of Hypercalcemia

Saline hydration is the first step of urgent care in the correction of hypercalcemia, diluting the serum calcium concentrations and increasing calcium removal in the kidneys. It is necessary to treat the underlying leukemia/lymphoma, through radiation therapy and chemotherapy. A number of drugs were used to control HM-associated hypercalcemia long-term. (43).

Bisphosphonates have been frequently used for the treatment of cancer patients with hypercalcemic, inherited spinal defects in infants and postmenopepausal and glucocorticoid patients with severe bone loss (44). Bisphosphonates are molecular analogs to pyrophosphoric acid. A standard treatment for HHM is the intravenous aminobisphosphonate (45).

The recent generation of bisphosphonated aminobisphosphonates containing nitrogen inhibites the metabolic process of farnesyl pyrophosphates (FPP) and geranylgeranyl pyrophosphates (GBPPs), result in lower isoprenylation of minute molecular G-proteins, comprising Ras. It resulted in the use of G-proteins. For osteoclastic behavior and survival, usable Ras signals are required (46). Bisphosphonates were also proposed as having a cytotoxic influence on T-cells contaminated with HTLV-1. Nonetheless, for cytototoxic effects in vitro and in vivo, high doses of bisphosphonates have been needed (47- 48).

Consequently, bisphosphonates gradually become highly concentrated in the bone and removed from circulatory and extracellular fluid. Low bone turnover, atrial fibrillation incidence and bone osteonecrosis complications occur due to bisphosphonate therapy (49). A novel bisphosphonate YM527 / ONO-5920 lowered the appearance and secretisation of MIP-1 as well as its impact on osteoclasts by inhibiting the transient development of phosphoryled phosphorylated ERK1/2 and function in mouse myeloma cell once stimulation of lipopolysaccharides (LPS) (49).

Growth of myeloma cells can be inhibited through bisphosphonates and may be prevented from osteolysis by reducing MIP-1 expression, because MIP-1-Arms have proven to have an essential part in osteolysis and cancer-cell development. It can also be the case with ATLL Pamidronate and zoledronic acid are widely used bisphosphonates (50).

For the treatment of multiple myeloma hypercalcemia and specific types of lymphoma, corticosteroids were used. Corticosteroids function by reducing the concentration of calcium in the gastrointestinal tract, raising bone resorption and rising urinary excretion. For patients with HM caused by solid tumors, corticoids are usually not active (50).

Conclusion

Hypercalcemia is more common in patients with advanced cancer. Fatal disease hypercalcemia typically presents with significantly higher calcium (ca^{++}) levels and so patients typically have severe indicative symptoms. The development of hypercalcemia in malignancy has many types including 1, 25-dihydroxyvitamin -D mediated-hypercalcemia, osteolytic metastases-related hypercalcemia and PTH-mediated hypercalcemia. The analysis must be comprising the patient's clinical history and physical inspection. In certain patients management of disease including calcitonin intravenous hydration, bisphosphonates, cinacalcet and prednisone. Patients having advanced stage renal disease and refectory sever hypercalcemia must be well-thought-out for hemodialysis. Hematologist or oncologist and psychiatrists would guide the choice of treatment for cancer and help patients and surgeons take care of the rest and discuss possible rest care option.

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