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Malignant hypercalcemia: clinical case and minireview

Summary

Malignant hypercalcemia is defined as the presence of high serum calcium concentrations in the context of tumor pathology. It is the most common cause of hypercalcemia in hospitalized patients with solid tumors or hematological neoplasms where the postulated mechanisms are the presence of bone metastases and / or the secretion of factors that activate resorption by tumor cells. It can be detected as a finding in the study of asymptomatic patients or be associated with severe clinical manifestations that require urgent treatment. The therapeutic approach must be carried out in an interdisciplinary way aimed at normalizing calcemia, being important the etiological diagnosis to adapt the therapeutic behavior in the long term avoiding future complications.

This article presents the case of a 43-year-old female patient immunosuppressed by HIV with a diagnosis of symptomatic hypercalcemia in the context of tumor pathology and bone metastases, her multidisciplinary diagnostic and therapeutic approach with a brief review of the topic.

Keywords: hipercalcemia, hipercalcemia maligna, metástasis oseas, bifosfonatos, denosumab

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Introduction

Malignant hypercalcemia is defined as the supra-physiological calcium concentration in the context of tumor pathology, either by tumors that metastasize in bone tissue or associated with the production of molecules by the tumor cell with the ability to activate bone resorption and increase calcemia. Calcemia levels can range from mild (10.5-12 mg/dl), moderate (12-14 mg/dl) or severe (greater than 14 mg/dl) usually associated with clinical manifestations that constitute an endocrinological emergency. This article presents the clinical case and interdisciplinary management of a patient admitted to the emergency unit with symptomatic malignant hypercalcemia, providing a brief review of pathophysiological mechanisms and therapeutic approach.

Clinical case

A 43-year-old female patient with a history of HIV with poor adherence to antiretroviral therapy, who consults the emergency department for pain, increased diameter of the left lower limb and functional impotence. It reports low back pain of 3 months of evolution adding in the last three weeks generalized weakness, hyporexia, weight loss, nausea, vomiting, and constipation.[1,2]

On physical examination, infra patellar edema was observed in the right lower limb with signs of positive homans and ollow, pain on palpation of both iliac crests with a slightly distended abdomen where an increase in abdominal tension is palpated at the the hypogastrium and right iliac fossa. The laboratory showed the following alterations: HTO 33% (VR: -40-46), Hb 10.8 g/dl (VR: 13-17), deterioration of renal function (creatinine 2.35 mg /dl (VR : 0.7-1.2), uremia 96 mg / dl (VR : 10-50) and creatinine clearence 27 ml/min), LDH 725 U / L , Hyperuricemia 15 mg / dl (VR: 1.5-7.0) and frank increase in calcemia (Calcemia 19.11 mg/dl VR: 8.6-10.2). Electrocardiogram is performed that shows sinus tachycardia, with shortening of the QT interval, without signs of acute ischemia.

The patient is evaluated in the first instance by the endocrinology service who establish treatment for severe symptomatic hypercalcemia with broad parenteral hydration, furosemide 20 mg c/12 hs and hydrocortisone 200 mg intravenous. They request to complete a study with phosphocalcium metabolism, 24-hour urine, bone remodeling markers (FAL, FAO, Beta Cross Lap), dosage of 25 OH Vit D and parathormone (PTHi). Doppler ultrasonography confirms the diagnosis of right popliteal femoro deep vein thrombosis and anticoagulation with low molecular weight heparin is initiated. Computed Tomography (CT) scan is performed where bulky abdominal tumor is observed with infiltration of the sacral cortical associated with multiple vertebral osteolytic images suggestive of secundarism (Figure 1-3).[3–6]

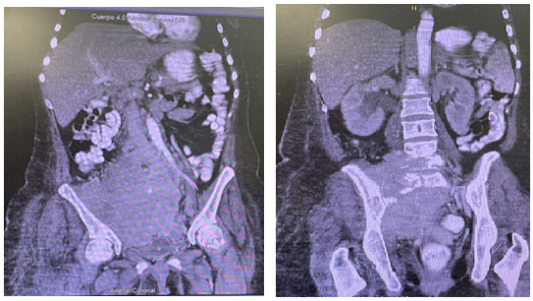

Figure 1 Voluminous image of density of soft parts in hypogastric region and right iliac fossa of 143 x 137 mm in contrasted abdominal CT (A). Right hydronephrosis and bone cortical involvement generating lysis of the right sacral aleron and lytic-looking images in the vertebral body of D2, L1, L4 and L5 (B).

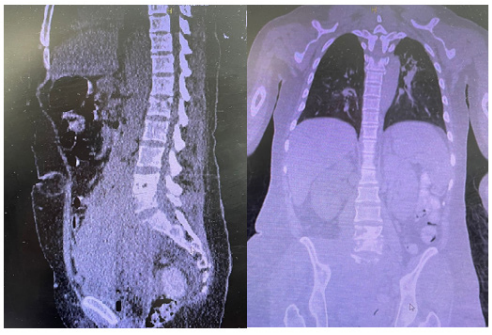

Figure 2 Osteolytic images at the sacroiliac level and in dorsolumbar vertebral bodies compatible with secundarism in non-contrast tomography; sagittal and coronal cut (A and B).

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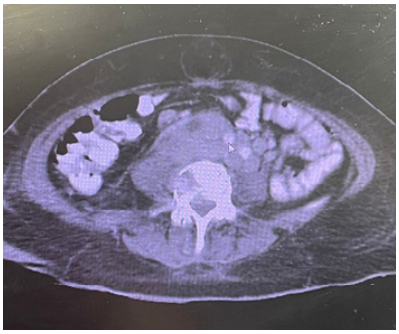

Figure 3 Abdominal tumor and retroperitoneal adenomegaly involving the iliac vessels.

Malignant hypercalcemia is confirmed in the context of abdominal tumor and bone metastases. The results of the phosphocalcium study show improvement in calcemia (12 mg/dl) and recovery of renal function after treatment with hypovitaminosis D (25OHD 13.68 ng/dl) and a sharp increase in markers of bone remodeling (FAL 260 VR: 40-130 and Beta Cross Lap 3.17 VR: <0.57). Vitamin D3 is supplemented with 100,000 IU every 15 days and plans treatment with bisphosphonates (Zoledronic Acid 4 mg/quarterly) with the aim of controlling calcemia and bone metastases. Bone lesions are evaluated by traumatology without evidence of spinal instability maintaining expectant management. Percutaneous biopsy is performed and the pathological diagnosis of high-grade B lymphoma is reached, continuing follow-up by hematology.

Review and discussion

The phenomenon of bone remodeling is the most powerful regulatory mechanism of calcemia, since bone tissue reserves 99% of the body's calcium. Osteoforming cells (osteoblasts and osteocytes) and springs (osteoclasts) are those involved in this phenomenon that allows the maintenance of bone mass. The main route of activation of remodeling is mediated by PTH although other cytokines and hormones can intervene in the activation of osteoclasts increasing resorption and calcemia. PTH acts on membrane receptors (PTHR) activating osteoblasts which release the soluble molecule RANK-L (KappaB nuclear factor activating receptor ligand). RANK-L interacts with its RANK receptor in precursor cells of osteoclasts favoring their differentiation to mature osteoclasts with activation of bone resorption. During the osteoformation process, osteoblasts increase the secretion of osteoprotegerin (OPG), a RANK-L inhibitory molecule that favors osteblastic activity with the deposit of new bone matrix. This phenomenon allows the maintenance of a stable bone mass throughout life having physiological imbalances at the expense of formation during growth and resorption during climacteric. Pathological situations such as neoplasms can alter bone remodeling with complications such as osteolysis and fractures and/or malignant hypercalcemia.

PTH is a hypercalcemiant hormone that not only activates bone resorption, but also mediates at the renal level the distal tubular reabsorption of calcium and activation of the enzyme 1α Hydroxylase (1αOHlase). It is responsible for catalyzing the conversion of 25OH Vitamin D, to its active form 1-25 OH vitamin D favoring the absorption of calcium in the small intestine. Other molecules involved in the regulation of the remodeling phenomenon are pro-inflammatory interleukins (IL-1, IL-6 and TNFα), prostaglandins, and hormones such as T3 and the PTH-related peptide (PTHrp). This molecule whose gene is located on chromosome 12 shares the similarity of the terminal NH2 end with PTHi that allows it to interact with PTH Type 1 receptors (PTH1R) generating a similar PTH effect.

Osteolithic metastases are associated with imbalance of remodeling at the expense of resorption, associated with bone loss, fragility, the possibility of pathological fractures and/or hypercalcemia with the clinical and metabolic consequences that this entails. The pathophysiological mechanisms associated with malignant hypercalcemia are:

Tumor cells that express and secrete RANK-L: the expression of RANK-L is described in mammary cells and T lymphocytes, therefore breast or hematological neoplasms can occur with tumor hypercalcemia mediated by secretion of RANK-L and direct activation of osteoclasts.

PTHrp synthesis: the PTH simil peptide can activate bone resorption with hypercalcemiante effect as well as fulfill other functions related to PTH such as renal tubular reabsorption of calcium and activation of vitamin D. This mechanism corresponds to 80% of the causes of malignant hypercalcemia associated with solid tumors such as the primary breast, lung and kidney. The ectopic secretion of PTHi by cells of tumors of the ovary, lung, stomach, pancreas or neuroectoderm derivatives has also been described. And although it is rare (less than 1% of the causes of primary hyperparathyroidism) it is worth mentioning parathyroid carcinoma as a cause of malignant hypercalcemia associated with PTHi.

Secretion of pro-inflammatory cytokines and growth factors (GFs): metastatic tumor cells that invade bone tissue can secrete interleukins and growth factors that locally activate osteoclast differentiation and resorption generating a vicious feedback loop that keeps hypercalcemia sustained. This mechanism prevails in osteolithic metastases or multiple myeloma where excess resorption generates bone trabecula loss, fragility and fractures in the context of hypercalcemia.

Calcitriol-mediated: associated with expression of the enzyme 1αOHlase by tumor cells. This enzyme converts vitamin D to its active form favoring the intestinal absorption of calcium with hypercalcemia. This mechanism is common in hematological neoplastics (myeloma, leukemias, lymphomas). It also explains hypercalcemia related to granulomatous pathologies such as tuberculosis and sarcoidosis.

These mechanisms can coexist for the same tumor pathology. For example, in breast cancer, hypercalcemia may be related to the synthesis of pro-inflammatory IL, RANK-L and/or PTHrp by metastatic tumor cells.

The diagnostic approach of any patient admitted for suspected tumor hypercalcemia should include a laboratory with complete phosphocalcic metabolism (calcemia, phosphatemia, ionic calcium), albumin (to calculate corrected calcium), PTHi and 25OHVitD. Add urinary parameters (calciuria, phosphaturia, creatinuria) and creatinine clearence. Associate blood count, hepatogram, glycemia, urea, creatinine and ionogram. It is important to include in the evaluation of the patient Electrophoretic Proteinogram, markers of bone remodeling formation (FAL and FAO) and resorption (Beta Cross Lap).

Calcemia values are also predictors of neoplastic etiology. Calcemias greater than 13 or 14 mg/dl give suspicion of tumor hypercalcemia. Similarly, the coexistence of skeletal clinical manifestations together with osteolithic images or pathological fractures. Malignant hypercalcemias are usually associated with low concentrations of PTHi as they are mediated by other independent

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PTH mechanisms (ILs, GFs, PTHrp, calcitriol) and excess calcium inhibits paratohormone synthesis in the parathyroid glands.

Bone deterioration, fragility and fractures are consequences of the direct effect of metastatic osteolysis but in malignant hypercalcemia we must remember the systemic side effects of the excessive increase in calcium sustained over time. Cardiac function should be monitored for changes secondary to hypercalcemia such as short Q-T interval, S-T segment elevation, and arrhythmias. There may be neurocognitive alterations (irritability, confusion, coma) and excess renal excretion of calcium impaired renal function. Gastrointestinal symptoms of nausea, vomiting and diarrhea can also be associated with acute pancreatitis and muscle manifestations such as fasciculations and / or myalgia. These were some of the clinical manifestations presented in the presented case that led to the presumptive diagnosis. A correct interrogation and clinical history together with the physical examination, allow to establish the presumptive diagnosis and guide complementary studies that direct the most appropriate therapeutic proposal in each case.

The treatment of the symptomatic patient should be established as a matter of urgency aimed at normalizing calcemia and remission of symptoms. General parenteral hydration guidelines should be administered by monitoring the patient's cardiac function and the use of loop diuretics (furosemide) or glucocorticoids can be added to the therapeutic plan. In hematologic neoplasms, such as the case presented, the calcitriol-mediated mechanism is probable and patients respond to glucocorticoid treatment by inhibition of vit D 1αOHlase.

Bisphosphonates are the drugs of choice for their powerful antiresorptive and apoptotic effect on osteoclasts, which has the particularity of being sustained over time allowing spacing application periods. The most commonly used route of administration is intravenous, since a more powerful therapeutic effect is achieved, being the drugs, zoledronic acid 4 mg or pamidronate 90 mg. It is essential to have the white blood cell count and assess the renal function prior to the infusion, since leukopenia or creatinine clearence less than 35 ml contraindicate the use of bisphosphonates. The bisphosphonate effect starts 48-72 Hs after application and becomes effective at approximately 7 days, for this reason we do not expect that calcemia immediately returns to normal but that the effect will be progressive and due to its high effectiveness we must be attentive to the appearance of transient hypocalcemia.

In cases where the use of bisphosphonates is contraindicated, denosumab 120 mg, a RANK-L inhibitor monoclonal antibody is indicated in tumor hypercalcemia. It is applied subcutaneously and has a more potent effect of controlling calcemia than bisphosphonates having described cases of hypocalcemia more frequently. The denosumab effect starts 3 days after application and can last up to 1 month.

Antiresorptives (bisphosphonates and denosumab) are effective both, control of calcemia and treatment of bone metastases protecting the patient from pathological fractures but their effect is transient. For this reason, treatment should be sustained over time by monitoring calcium and vitamin D concentrations before each application of antiresorptive. Direct antitumor effects of zoledronic acid (antiangiogenic and activator of cytotoxic T lymphocytes) and indirect effects as an inducer of apoptosis and decreasing the bone adhesion of tumor cells and the invasion of the extracellular matrix have also been described. As for denosumab, its beneficial antitumor effect would be linked to breast cancer whose cells express RANK-L.

In calcitriol-mediated hypercalcemias, the use of glucocorticoids is useful for their ability to inhibit vit D 1αOH lasa and hypercalciuric effect. The proposed drugs are hydrocortisone in high doses of 200-400 mg/day or methylprenisone 60 mg/day during the first week of treatment. The concept of the reversible effect of treatment is fundamental because if sustained measures are not continued while the patient continues with active pathology, the possibility of recurrence of malignant hypercalcemia is common.[7–9]

Conclusion

Tumor hypercalcemia is a condition of complex management, which must be addressed in a multidisciplinary way where the focus of the treating physicians must be placed on the correct approach of the patient tending to resolve in the acute urgency and establish etiological and differential diagnoses in order to adapt the correct treatment in the long term to avoid complications and recurrences.

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None.

Conflicts of interest

The authors declare no conflicts of interest.

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