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Case Report

Primary Hyperparathyroidism, Osteogenesis Imperfecta and Breast Cancer: A Complex Case Report and Literature Review

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Abstract

Primary Hyperparathyroidism **(PHPT)** is the most common cause of hypercalcemia. It also may present with osteoporosis, hypercalciuria, vertebral fractures and nephrolithiasis. Moreover, Breast Cancer **(BC)** patients receiving treatment with aromatase inhibitors present an increased risk of accelerated bone loss. We present the clinical case of a 78-year-old woman who, during hospitalization for pneumonia, developed new-onset hypercalcemia and hypophosphatemia and was diagnosed with PHPT caused by an adenoma. She had also previously been diagnosed with breast cancer, for which she underwent total mastectomy, and is currently undergoing chronic treatment with Letrozole. Among other comorbidities, she suffered from osteogenesis imperfecta, chronic renal insufficiency due to a congenital malformation that functionally excluded the left kidney, pulmonary hypertension, massive mitral insufficiency, heart failure with preserved ejection fraction, and atrial fibrillation. She had also suffered three vertebral fractures. The patient presented with sarcopenia. Our objective is to review the clinical management of this complex case, where parathyroidectomy was contraindicated due to all the severe comorbidities, and left nephrectomy was postponed to a mitral cardiac intervention procedure, and to analyze the literature in order to identify the best treatment to manage this type of multifactorial hypercalcemia.

Keywords: Hypercalcemia; Primary hyperparathyroidism; Osteogenesis Imperfecta; Breast Cancer; Bisphosphonates; Denosumab

Introduction

When hypercalcemia, or elevated Serum Calcium Levels **(SLCs),** occurs, especially if associated with hypophosphatemia, it is necessary to investigate for Primary Hyperparathyroidism **(PHPT),** a condition that may also cause osteoporosis, vertebral and non-vertebral fractures, nephrolithiasis, and hypercalciuria. Another cause of osteoporosis and low bone mineral density **(BMD)** is Breast Cancer **(BC),** due to its impact on body composition (percentage of body fat, distribution of fluids, proteins and muscles). In addition, age, duration of chemotherapy treatment, especially with aromatase inhibitors [1] and menopausal status are related to low BMD [2].

Hypercalcemia may also present in BC patients as result of metastasis or paraneoplastic syndrome characterized by ectopic Parathyroid Hormone Related Protein **(PTHrP)** production [3]. Besides that, another rare cause of low BMD is Osteogenesis Imperfecta **(OI),** an inherited skeletal dysplasia caused in 90% of cases by mutations in COL1A1 and COL1A2, each of which correspond to α1 and α2 chains of type I collagen. It can show in several grades of severity and many phenotypes; each one is characterized by bone fragility, but worst cases present with skeletal deformities, dental and craniofacial abnormalities, muscle weakness, hearing loss, respiratory and cardiovascular complications [4]. While there are few pieces of evidence in the literature about the co-existence of BC and PHPT [5-7], or BC and OI [8-10], the simultaneous presence of the three aforementioned conditions is very rare, if not unique, as long as we know.

Clinical Presentation

A 78-year-old woman was admitted to the Geriatric Unit of the Federico II University Hospital for pneumonia in poor general condition and with evident skeletal deformities. Reconstruction of the patient's medical history was very difficult due to the limited social support and low level of education. Her clinical background included chronic kidney disease secondary to a congenital malformation with a left nephrostomy placed in a functionally excluded kidney, as well as, pulmonary hypertension, severe mitral insufficiency with surgical indication, heart failure with preserved ejection fraction and atrial fibrillation.

The multidimensional geriatric evaluation showed the presence of sarcopenia and a moderate degree of frailty (Clinical Frailty Scale 6/9). After a few days of hospitalization, it was discovered that the patient was affected by type I OI and reportedly had no fractures in childhood. Ten years earlier, she had undergone mastectomy for breast cancer, currently on treatment with Letrozole and Denosumab (DMab) (daily and every six months respectively) for secondary prevention of fractures (BMD 0.650 g/cm2, T-score -4.4 and history of 3 vertebral fractures with an overall estimated FRAX of 76%), because she could not tolerate bisphosphonates due to the chronic kidney disease.

During hospitalization, the patient developed acute pulmonary oedema, which required her transfer to the intensive care unit. Soon after recovery and her return to our department, new-onset hypercalcemia and hypophosphatemia were found. She then underwent thyroid and parathyroid ultrasound and subsequently a thyroid scintigraphy, which led to the diagnosis of Primary Hyperparathyroidism **(PHPT)** caused by an adenoma. Due to the severe burden of comorbidities, parathyroidectomy was contraindicated. Hypercalcemia remained asymptomatic but rapidly led to a shortened QT interval requiring intervention with a single intravenous dose of Zoledronic Acid and initiation of Cinacalcet 30 mg daily. Hemodialysis was not required.

Discussion

In this complex clinical case, it was necessary not only to intervene on the severity of hypercalcemia to prevent fatal electrophysiological consequences, but also to understand whether chronic therapy was appropriate since parathyroidectomy was contraindicated due to the high surgical risk. It was essential to achieve an endocrine balance and at the same time prevent the risk of femoral fracture. As is known in elderly comorbid patients, this event seriously affects the health status and the Health-related Quality of Life **(HRQoL),** and most patients do not return to pre-fracture levels of performance [11]. Since it hasn't been possible to determine whether our patient has ever undergone a specific therapy for OI, we assume that her chronic therapy with DMab was established starting from the BC in aromatase inhibitors treatment, referring to Italian Drug Administration Agency (AIFA- Agenzia Italiana del FArmaco), specifically Note 79 which regulates Bisphosphonates and other drugs in primary and secondary prevention of fractures [12], which indicates that in chronic kidney disease with a single functional kidney, chronic therapy with bisphosphonates (first choice) was contraindicated.

So, we had to evaluate whether the established therapy with DMab was appropriate and feasible also for the other two coexisting conditions. Reviewing the literature on the pharmacological strategies in OI [4,13,14], Bisphosphonates still remain the first therapeutic choice while the efficacy of DMab is not so clear [15], although its effect seems to be similar to bisphosphonates, as its anti-RANKL activity can achieve osteoclast inhibition even with a shorter duration of action. However, discontinuation of DMab can lead to severe rebound hypercalcemia [16], which represented a

significant challenge in our clinical case due to the coexistence of Primary Hyperparathyroidism **(PHPT).** In most of the literature, this adverse effect is considered within the differential diagnosis of PHPT [17], whereas specific data on rebound hypercalcemia following DMab withdrawal in patients with confirmed PHPT are limited [16].

Nevertheless, we identified some evidence suggesting that DMab may exert a protective effect on bone in patients with PHPT [18-20], supporting the rationale for its continuation. Furthermore, Zhang et al., in their systematic review, reported that DMab appears to reduce serum calcium levels as early as the third day after administration, maintaining this effect for approximately 14 days before it diminishes [21]. Both of these effects can be explained by considering the pathophysiology of PHPT and the targeted mechanism of action of DMab on the RANK/RANKL pathway. Parathyroid Hormone **(PTH)** stimulates osteoblasts, which in turn promote osteoclast activation, leading to increased calcium release into the bloodstream. This specific process is counteracted by DMab, which inhibits the RANKL pathway and thereby suppresses bone turnover.

Finally, to complete our review, we also extended the research to new therapeutic horizons such as Romosozumab, a monoclonal antibody that inhibits sclerostine. Although we identified limited evidence regarding its use in OI [22,23], to the best of our knowledge, no clinical data are currently available on its use in patients with PHPT or bone conditions related BC. This highlights the need to extend clinical research and trials to these special populations.

Conclusions

As far as we know, there are no reports in the literature of cases with the simultaneous coexistence of all three pathologies. This made the therapeutic management of this complex scenario particularly challenging, necessitating multiple consultations, a thorough literature review, and the integration of diverse clinical experiences. By comparing and integrating therapeutic protocols for each condition, DMab emerges as the preferred option after bisphosphonates which are contraindicated for long-term use in patients with chronic kidney disease. DMab has demonstrated both a protective effect on bone and a calcium-lowering effect.

However, it is crucial to emphasize that DMab should never be discontinued, as rebound hypercalcemia in these patients, who are not eligible for surgery, could be life-threatening. On the other hand, it may be necessary to reassess the continuation of chronic Aromatase Inhibitor **(AI)** therapy, particularly considering the patient's life expectancy.

Lastly, it may be interesting to extend clinical trials of Romosozumab in those patients affected by OI plus PHPT, or OI plus BC.

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