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Development of Hypocalcemia Due to Targeted Therapies

Hedefe Yönelik Tedavilere Bağlı Gelişen Hipokalsemi

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Abstract

Novel biological agents are available for the treatment of malignancies, and apart from their utility, they may also have several side effects. The effects on the endocrine system are frequently observed, among which thyroid dysfunctions are common and well-characterized, whereas parathyroid dysfunctions are rare and not well characterized. Herein, we describe two of our patients that displayed hypoparathyroidism and were treated with epidermal growth factor receptor (EGFR) inhibitor erlotinib, vascular endothelial growth factor receptor, and EGFR inhibitor vandetanib.

Keywords: Erlotinib; vandetanib; hypocalcemia; hypoparathyroidism

Özet

Malignitelerin tedavisinde kullanılmakta olan yeni biyolojik ajanların yararlarının yanı sıra, birtakım yan etkileri de mevcuttur. Endokrin sistem üzerine sıklıkla etkiler görülmektedir ve bu etkiler arasında tiroid disfonksiyonu en sık olan ve en iyi tanımlanmış etki iken; paratiroid disfonksiyonu nadirdir ve iyi tanımlanamamıştır. Burada, epidermal büyüme faktörü reseptörü (EBFR) inhibitörü erlotinib ve hem vasküler endotelyal büyüme faktör reseptörü hem EBFR inhibitörü olan vandetanib ile tedavi edilen 2 olgumuzda gelişen hipoparatiroidizm tablosunu tanımladık.

Anahtar kelimeler: Erlotinib; vandetanib; hipokalsemi; hipoparatiroidizm

Introduction

Due to their inhibitory effect on proliferation, motility, apoptosis, and metastasis, the epidermal growth factor receptor (EGFR) inhibitor erlotinib and vascular endothelial growth factor receptor (VEGF) and EGFR inhibitor vandetanib are viable therapeutic options for the treatment of advanced non-small cell lung carcinoma (NSCLC) and thyroid cancer, respectively (1).

NSCLCs and medullary or differentiated thyroid carcinomas (MTC and DTC) may show bone metastasis along with bone pain, elevated serum calcium, or elevated alkaline phosphatase levels.

We present the interesting cases of two patients who were diagnosed with NSCLC and MTC with bone metastasis. Both were treated with EGFR inhibitors and presented at our outpatient clinic with hypocalcemia as a result of hypoparathyroidism.

Case Reports

Case 1

A 48-year-old Caucasian woman was admitted to our outpatient clinic with asymptomatic hypocalcemia. She described her history of total thyroidectomy due to micropapillary thyroid carcinoma (PTC) five years ago, and was not treated with radioactive iodine ablation. She was indicated to be in remission for PTC and was receiving thyroid hormone suppression therapy.

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Two years ago, she was diagnosed with metastatic (bone) lung adenocarcinoma and was receiving erlotinib treatment for the past six months. She was referred from the oncology department due to hypocalcemia. She had a body mass index (BMI) of 33.6 kg/m^2. Physical examination on admission was unremarkable, except for her obesity and a positive Chvostek sign. Biochemical analysis showed severe hypocalcemia with a corrected calcium level of 7 mg/dL (normal range 8.2-10.2). Other laboratory findings associated with hypocalcemia, such as the levels of phosphorus [4 mg/dL (2.5-4.5)], 25 (OH)-vitamin D [28 ng/mL (20-50)], and magnesium [2 mg/dL (1.8-2.6)], were within the normal reference ranges, and although the parathormone levels (PTH) were within the normal reference range despite hypocalcemia [intact PTH 35 ng/mL (12-65)], they were considered to be inappropriately low for the observed calcium level.

Hypocalcemia was initially thought to be associated with her neck surgery, but after evaluation of her calcium levels after the surgery, it was observed that the calcium levels declined after initiation of erlotinib therapy for NSCLC with osteolytic bone metastasis. Her historical calcium levels ranged in the upper normal reference range due to bone metastasis (8.9-9.8 mg/dL) before initiation of erlotinib therapy, and remained so until the completion of four months of erlotinib therapy. For the last two months, her calcium levels were observed to be within the medium and lower normal of the reference range. There was no information about her PTH levels before admission to the endocrinology department.

The patient probably did not receive bisphosphonate therapy for bone metastasis, which could also result in hypocalcemia. Denosumab was given for bone metastasis instead of bisphosphonates. Calcium and calcitriol replacement therapy was initiated for hypocalcemia and normal calcium levels were achieved. With the continuation of erlotinib therapy, bone metastasis neither progressed nor resolved, and these replacement therapies were synchronously given because of existing hypoparathyroidism and hypocalcemia. She is still on 150 mg/day of erlotinib therapy.

Case 2

A 56-year-old man was diagnosed with MTC ten years ago and had neck surgery including total thyroidectomy and dissection of the central lymph node. Four years ago, the disease progressed and extensive metastases occurred in the lung, liver, and bone. After a couple of months of therapy with vandetanib, a multi-kinase inhibitor targeting EGFR, RET, and VEGFR, the biochemical analysis revealed extremely low calcium levels [corrected calcium 4.9 mg/dL (8.2-10.2)]. The patient showed severe muscle cramps in his hands, with slight numbness and tingling in the perioral area.

The levels of magnesium (2.2 mg/dL) and phosphorus (4.2 mg/dL) were within the normal reference range, while level of 25(OH) vitamin D [5 ng/mL (20-50)] was low, and that of PTH [34 ng/mL (12-65)] was within the normal range despite severe hypocalcemia. Like the first case, we observed hypoparathyroidism after the initiation of vandetanib (300 mg once daily) treatment. His calcium levels were within the normal reference range (9-9.5 mg/dL), and his previous PTH levels were unknown. Calcium supplements and calcitriol treatment were initiated to maintain a normal calcium level. In addition to vandetanib therapy, he also received denosumab therapy (120 mg subcutaneously once every four weeks) for bone metastasis. He died after eight months of therapy, because of septicemia due to pneumonia.

Discussion

Targeted therapies with EGFR have become a cornerstone in the treatment of several metastatic cancers. A majority of patients show general side effects of EGFR, although endocrine-related adverse effects are comparatively rare. Endocrine-related adverse effects of these agents include thyroid dysfunction, gonadal dysfunction, adrenal dysfunction, or disorders of glucose metabolism. However, scarce information is available on parathyroid dysfunction.

Although recent reports have described secondary hyperparathyroidism in patients taking kinase inhibitors, side effects such as hypoparathyroidism and hypocalcemia were also reported.

In fact, PTH receptor 1 and the calcium-sensing receptors are the members of the G protein-coupled receptor (GPCR) superfamily and do have a direct relation with tyrosine kinases. It is hypothesized that there may be a cross-talk between certain receptor tyrosine kinases and GPCRs (2). parathyroid cells express EGFR, which then mediates the stimulation of parathyroid cellular proliferation. Erlotinib was found to inhibit parathyroid growth and decrease the levels of proliferating cell nuclear antigen (PCNA) and TGF-α (3). Apart from changes in cellular proliferation, apoptosis may also play a role in parathyroid-related side effects.

It was shown that the activation of EGFR promotes parathyroid hyperplasia and enhances the parathyroid levels in rats with kidney disease. Therefore, the inhibition of EGFR with erlotinib was observed to prevent the growth of parathyroid cells, self-promotion of the Transforming Growth Factor-α (TGFα), and reduction of the 25 (OH) vitamin D receptor (4,5).

EGFR inhibitors can cause hypomagnesemia accompanied by wasting of renal magnesium (Mg), due to the inhibition of transient receptor potential melastatin 6 protein channel (TRPM6), which is responsible for Mg handling (6). However, we did not observe any episodes of hypomagnesemia in our patients.

An association was observed between parathyroid hormone-related protein (PTHrP) gene and EGFR signaling (1). The treatment with EGFR inhibitors has been demonstrated to decrease the production and gene expression of PTHrP (40-80%), as well as the total plasma calcium concentrations in hypercalcemic mice (7).

A sudden decline in calcium levels after initiating EGFR inhibitors, in contrast to the evidence of bone metastasis in these cases, indicated that these agents may have prevented parathyroid cell growth, and the resulting decreased PTH levels led to hypocalcemia.

In order to the best of our knowledge, although several reports have demonstrated the hypocalcemic effects of erlotinib monotherapy when compared to erlotinib and emibetuzumab combination therapy (8), and vandetanib therapy when compared to placebo (9), none have described the probable and exact etiology of hypocalcemia. The cases described in our study are the first in the literature to demonstrate the occurrence of hypocalcemia due to hypoparathyroidism from the use of erlotinib and vandetanib, despite both the patients having widespread bone metastasis. Although a history of neck surgery may be a reason for hypoparathyroidism in these cases, the possible effects of these agents on parathyroid glands should not be underestimated. A prospective controlled study may prove our hypothesis. Until then, hypocalcemia should be considered as a possible side effect of EGFR inhibitors, especially in patients with a history of neck surgeries.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Asena Gökçay Canpolat; Design: Asena Gökçay Canpolat; Control/Supervision: Sevim Güllü, Murat Faik Erdoğan; Data Collection and/or Processing: Asena Gökçay Canpolat, Şule Canlar, Berna İmge Aydoğan; Analysis and/or Interpretation: Asena Gökçay Canpolat; Literature Review: Asena Gökçay Canpolat; Writing the Article: Asena Gökçay Canpolat; Critical Review: Murat Faik Erdoğan; References and Fundings: Asena Gökçay Canpolat.

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